Multisite pain and falls in older people

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Submitted in fulfilment of the requirements of the degree of Doctor of Philosophy

Date of Submission: March 2018

Research Institute for Primary Care & Health Sciences

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Abstract

Falls are a common occurrence in older people and multisite pain has been identified as a potential falls risk factor in this age group. This thesis aims to describe the relationship between multisite pain and falls in community-dwelling older people.

A systematic review identified 20 studies investigating multisite pain and falls. Meta-analysis showed multisite pain increased the odds of falling.

Data from the North Staffordshire Osteoarthritis Project, a prospective cohort study of community-dwelling adults aged ≥50 years with follow ups at three and six years, was used. Survey data was linked with general practice (GP) records, Hospital Episode Statistics (HES) and Office for National Statistics mortality data. Logistic regression tested the relationship between multisite pain and risk of self-reported falls in 4386 participants with complete data. Survival analysis tested the relationship between multisite pain and risk of GP or HES recorded falls in 11,375 participants. Analyses were adjusted for confounders and putative influencers of the pain-falls relationship.

Multisite pain most strongly predicted future self-reported falls, followed by GP recorded falls. Multisite pain was not associated with HES recorded falls. Increasing age, being female, increasing number of medications used and strong analgesic use predicted all future falls; increasing cognitive complaint and previous self-reported fall additionally predicted GP recorded falls and all confounders and

putative influencers predicted self-reported falls and had a significant association with multisite pain.

These data suggest that multisite pain is an independent risk factor for self-reported falls. In addition, multisite pain is a likely influencer of the relationship between other risk factors and future falls.

Primary care should proactively identify older adults with multisite pain due to their increased risk of falling and instigate falls prevention management according to current guidelines. Future research will establish the impact of pain management interventions on future risk of falls.

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Acknowledgements

I would like to thank my supervisors Professor Christian Mallen and Dr John McBeth for their guidance and support throughout this process, from developing the initial proposal through to thesis submission.

Thanks must also go to several people whose contributions have been invaluable along the way. Rhian Hughes (support through the data acquisition process), the Research Centre Health Informatics Team and Dr Elaine Thomas (for assistance with data linkage), Dr Reuben Ogollah (for assistance with database preparation and data management), Dr John Belcher (statistical advice), Dr Nadia Corp (systematic review search strategy), Dr Lorna Clarson (systematic review study assessment and quality appraisal), the Research Users Group at Keele University (proposal development), and Professor Peter Croft for providing a continued source of inspiration and enthusiasm. Many thanks also to my clinical colleagues who have been supportive of this process.

This PhD would not have been possible without the unconditional and unwavering support of my family. Thank you Paul, Mum, Dad, and Natalie; I am eternally grateful for all you have helped me with over the past seven years. Finally, thank you to my lovely children, Ernest and Astri, for your understanding and patience; this PhD is dedicated to you.

Glossary

95% CI	95% confidence intervals
ABS-SIP	Alertness behaviour subscale of the Sickness Impact Profile
ACR	American College of Rheumatology
APC	Admitted patient care
BGS	British Geriatrics Society
BMI	Body mass index
BNF	British National Formulary
CCI	Charlson Comorbidity Index
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and the Allied Health Literature
CiPCA	Consultations in Primary Care Archive
CKD	Chronic Kidney Disease
D&L	DerSimonian & Laird
DoH	Department of Health
GP	General Practitioner
GPRD	General Practice Research Datalink
HADS	Hospital Anxiety and Depression subscale

HES	Hospital Episode Statistics
HR	Hazard ratio
ICD	International Classification of Disease
IMD	Index of Multiple Deprivation
KW	Kruskal Wallis
LR	Likelihood ratio
LREC	Local research ethics committee
NHS	National Health Service
NHSIC	NHS Health and Social Care Information Centre
NICE	National Institute for Health and Care Excellence
NIGB	National information governance board
NIHR	National Institute for Health Research
NorStOP	North Staffordshire Osteoarthritis Project
NPS	Number of pain sites
NSAID	Non-steroidal anti-inflammatory drug
ONS	Office for National Statistics
OPCS-4	The Office for Population, Censuses and Surveys: Classification of Interventions and Procedures version 4
OR	Odds ratio

PR	Prevalence ratio
ProFaNE	Prevention of Falls Network Europe
QOF	Quality outcomes framework
QUIPS	Quality in prognostic studies
RCGP	Royal College of General Practitioners
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36
SIP	Sickness Impact Profile
THIN	The Health Improvement Network
tvc	Time varying covariates
UK	United Kingdom
US	United States of America
WHO	World Health Organisation

Chapter 1 Context of the thesis

1.1 Overview

This chapter sets the context of the thesis. A brief rationale is presented, followed by a list of thesis aims and objectives; a chapter layout is also presented to aid navigation through the thesis.

1.2 Context

I began my clinical academic career in 2006 when I completed the new Academic Clinical Foundation Year 2 training at Keele University and University Hospital North Staffordshire. I undertook a research project and started to develop my own interests in academic medicine. My research interest continued throughout my Academic Clinical Fellowship (ACF) in General Practice and I completed an MPhil degree in health sciences research.

I developed my interest in epidemiology and medicine for older people within the context of primary care during my ACF and, after witnessing the many consequences of falls and recognising their subsequent burden, I proposed a research project exploring the relationship between pain and falls in order to try to reduce the risk of falls in older people. I was awarded a Doctoral Research Fellowship from the National Institute of Health Research and commenced the work for this thesis after completing my ACF and obtaining my Certificate of Completion of Training in General Practice in 2011.

I have continued to work as a part time general practitioner throughout the Doctoral Research Fellowship and consequently the thesis retains a clinical focus,

with my conclusions and recommendations aimed at practising health professionals and policy makers.

1.3 Thesis rationale

Falls become increasingly common in advancing age and bear significant consequences for individuals, families and wider society. The UK population is ageing; falls are therefore occurring more often and are consequently more costly. There are many well-documented risk factors for falls that form national and international falls prevention guidelines, for example the World Health Organisation's Falls Prevention guidance published in 2007 (World Health Organisation, 2007). Despite widely published guidance, falls continue to impact on the daily lives of older people and create a financial burden for health and social care; novel ways of preventing falls must therefore be sought to reduce older people's risk of falls. Pain occurring in multiple body locations (also termed 'multisite pain') has been identified as a new risk factor for falls in a small cohort of older adults in the United States of America (Leveille et al, 2009). This thesis seeks to further examine the relationship between multisite pain and falls in a UK-based population of community dwelling older adults and make recommendations for health professionals and policy makers concerning falls prevention.

1.4 Thesis aims

The aim of this thesis is to describe the relationship between multisite pain and falls in older people. To address this aim, the thesis will meet the following objectives:

i) To describe the prevalence of self-reported falls, falls that require primary health care attendance and falls that require hospital admission in a population-based sample of community-dwelling older people;

ii) To test the hypothesis that older people with multisite pain are more likely to experience a future self-reported fall than older people with no pain;

iii) To test the hypothesis that older people with multisite pain are more likely to seek primary health care for a future fall than older people with no pain;

iv) To test the hypothesis that older people with multisite pain are more likely to be admitted to hospital as a result of a future fall than older people with no pain.

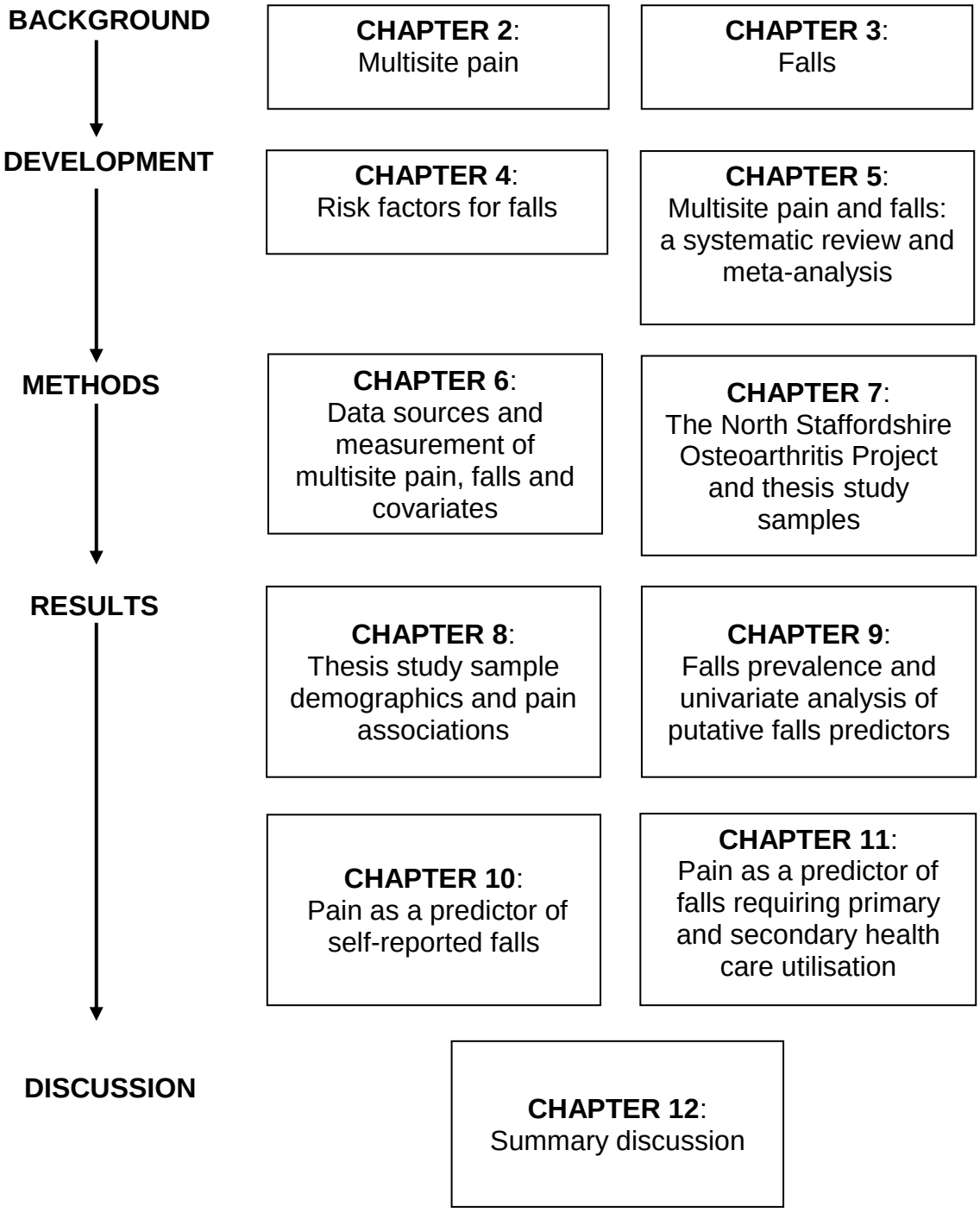
1.5 Thesis organisation

The thesis is organised into Chapters, as demonstrated in figure 1.1. Relevance to clinical practice is discussed where necessary throughout the thesis and summarised in Chapter 12.

1.6 Chapter summary

This chapter has set the thesis context, outlined the hypotheses and given a chapter overview. The background chapters will now describe multisite pain and falls in greater detail.

Figure 1.1 Thesis organisation



Chapter 2: Multisite pain

2.1 Overview

This chapter introduces the concept of pain, including both a broad definition of pain and a more focused definition of multisite pain. The epidemiology of pain is presented and the role of general practice in managing pain is summarised to provide clinical context to this thesis.

2.2 Definition of pain

Pain is defined as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* (Merskey & Bogduk, 1994). Experiencing pain is necessary for survival (Patel, 2010). Neural pathways are activated when the body is exposed to a noxious stimuli and a behavioural response is triggered to remove the body from potential danger (Patel, 2010). Congenital insensitivity to pain is a rare genetic condition, first described by Dearborn's case study in 1932, which causes loss of nociceptors and thus leads to multiple injuries and death as a result of the inability to feel and react to pain (Golshani et al, 2014).

Pain becomes problematic when it is no longer part of an essential human survival reaction. For example, pain that persists beyond an initial injury, or in a chronic disease process, for example knee pain that persists in osteoarthritis. Thus follows definitions of pain based on time-frame and utility. '*Acute pain'* does not overwhelm the body's responses and resolves in days or weeks (Loeser & Melzack, 1999); it is therefore considered a useful response that reduces the risk

of ongoing injury. *'Chronic pain'* has been recognised as 'pain which persists past the normal time of healing (Bonica, 1953 in: Merskey & Bogduk, 1994). In practice, this may be less than one month or more than six months depending upon the likely cause of the pain, for example nerve damage is likely to take longer to heal than a skin laceration (Merskey & Bogduk, 1994). This thesis uses a definition of 'pain on most days in the last four weeks' (described in Chapter 6). Although not conforming to the dominant definition of chronic pain lasting for more than three months (McBeth et al, 2010), this measure is likely to capture primarily chronic-type pain in those reporting a widespread pattern of pain, since once a widespread pattern is established, it is unlikely to resolve over time (Papageorgiou et al, 2002); pain over the life course is discussed further in Section 2.3.5.

2.3 Multisite pain

2.3.1 Defining multisite pain

Pain can be experienced in any part of the body; when pain is experienced in more than one location it is termed 'multisite pain'. Experiencing multisite pain is more common than experiencing single site pain. In their population-based cross-sectional survey of pain amongst an adult Dutch population, Picavet and Schouten (2003) reported the majority of those reporting pain reported pain at more than one site; the 12 month period prevalence of pain in one site was reported as 24.5%, pain at 2 or 3 sites was 29.4% and pain at four or more sites was 20.6%; thus the period prevalence of multisite pain was twice that of single site pain (Picavet & Schouten, 2003).

A subsequent UK population-based cross-sectional survey by Carnes et al (2007) reported that, from 2445 adults aged 18 years and older, 45% reported pain for more than half the days in the last year. Of those reporting pain, 25% reported single-site pain, 52% reported pain in two, three or four sites, 18% had pain in five, six or seven sites and 4% reported more than eight sites of pain; therefore about three-quarters of the pain sample reported multisite pain (Carnes et al, 2007).

2.3.2 Associations with multisite pain in the general population

2.3.2.1 Health-related functioning

Multisite pain has a significant impact on individuals. It is associated with poor health-related functioning. Saastamoinen et al (2006) investigated the impact of pain (duration, pain location and number of pain sites) on health-related functioning in 5829 Finnish employees aged 40–60 years (Saastamoinen et al, 2006). Saastamoinen et al, (2006) used the Short Form 36 (SF-36) to measure eight domains of physical and mental health functioning and well-being and found that, when compared with pain-free individuals, those with pain had significantly poorer functioning levels. The number of pain sites had the greatest effect on functioning levels with those reporting four or more pain sites functioning significantly worse than those with no pain. The acute or chronic nature of the pain and the location of pain only modestly affected functioning (Saastamoinen et al, 2006).

Kamaleri et al (2008) undertook a cross-sectional survey of 3325 adults aged 24–76 years residing in Norway to further explore the functional impact of localised and widespread musculoskeletal pain. Respondents were asked to indicate whether they had experienced pain in the last week, and where the pain had occurred using ten predefined body sites. Not only did the study confirm that pain was associated with functional limitations and that those with more pain had worsening levels of functional ability, there appeared to be an almost linear relationship between an increasing number of pain sites and increasing levels of functional ability, even when adjusted for age and sex (Kamaleri et al, 2008).

2.3.2.2 Work-related disability

Multisite pain is also associated with future work-related disability. A cohort of 1354 working age people from Kamaleri's 2008 cross-sectional survey were followed over 14 years and a strong dose-response relationship between the number of pain sites at baseline and future work-related disability was demonstrated (Kamaleri et al, 2009). This finding has important economic consequences for individuals and for society. Work-related disability prevents workers from fulfilling job roles and can lead to lost days from the workplace due to sickness absence. Sickness absence impacts upon workplace productivity and, if sickness absence is prolonged, requires financial support from central agencies, for example disability and sickness benefits paid by the UK Government. It is widely recognised that being employed improves individuals' health and well-being (Waddle & Burton 2006), thus unemployment is detrimental. Mclean et al (2005) reviewed the evidence for worklessness and health and reported a strong relationship between psychiatric morbidity and unemployment; complex

relationships between worklessness, poverty, poor health and mortality were also highlighted (McLean et al, 2005). Work-related disability as a consequence of multisite pain is therefore a considerable problem, particularly if long-term sickness absence and worklessness follow.

2.3.2.3 Mortality

The presence of multisite pain has also been associated with an increased risk of death from cancer, cardiovascular disease and all-cause mortality. McBeth et al (2009) conducted a cohort study of 4515 people aged 16 years and over, assessing pain status (no pain, number of pain sites, regional pain and widespread pain) at baseline and vital status (whether respondents were alive or dead) at 8 years. A greater number of pain sites was associated with increased risk of death from cancer (mortality rate ratio of 1.06 (95% CI 1.01-1.10)) or cardiovascular disease (mortality rate ratio 1.02 (95% CI 0.99-1.1)) (McBeth et al, 2009). A more recent systematic review exploring this association found that the presence of multisite pain increased the risk of all-cause mortality and cancer and cardiovascular-related deaths, although these associations were not statistically significant and the heterogeneity between studies was high (Smith et al, 2014).

2.3.3 Multisite pain as a continuous measure

Health-related physical functioning and future work-related disability have a linear relationship with the number of pain sites; the greater the number of pain sites, the greater the negative impact on physical functioning and work-related disability. It may therefore be useful to consider multisite pain as a continuous measure, with

the number of pain sites representing a continuum of the pain spectrum as proposed by Croft (2009).

This approach mirrors Rose's view that diseases should not be dichotomised into disease presence or absence (Rose, 1992). Instead, such variables need to be considered in continuous distributions to take account of the incremental increased risk of experiencing a poor outcome associated with each incremental increase in the variable (Rose, 1992; Croft, 2009). For example, the risk of myocardial infarction increases as the blood pressure rises and the risk of poor health-related physical functioning increases as the number of pain sites increases. Thus multisite pain is considered as a continuous variable in this thesis as detailed in Chapter 6.

2.3.4 Multisite pain as an ordinal measure

Taking the concept of multisite pain as a continuum, points on this continuous scale can be selected and an ordinal measure created with the categories i) no pain; ii) single site pain; and iii) widespread pain.

This ordinal measure represents a measure of how widespread the pain is. Widespread pain has a specific definition: "pain that affects multiple (including non-joint) sites in the body" (McBeth et al, 2014). How widely spread the pain is (termed 'widespreadness' in this thesis) is defined using the American College of Rheumatology (ACR) criteria for fibromyalgia, a widely recognised classification system for widespreadness (Wolfe et al, 1990). This classification requires participants to have pain in locations above and below the waist, on the right and left sides of the body and in the axial skeleton (Wolfe et al, 1990). Thus the ACR

widespread pain criterion is a more stringent measure of widespreadness than a simple count of pain sites. For example, it would be possible to report only five sites of pain (the right wrist, right hand, left knee, left foot and lower back) to be classified as 'widespread pain', yet one could report six sites of pain that could be further defined as regional shoulder pain with associated referred pain (reporting pain at the neck, left upper arm, left scapula, left elbow, left wrist and left hand).

Using the ACR definition of widespread pain to classify respondents' pain moves beyond a simple count of painful body sites towards a classification that carries with it connotations of chronic widespread pain syndromes such as fibromyalgia. Using this more extreme form of multisite pain may reveal stronger associations with detrimental outcomes than using a simple count of pain sites since widespread pain has been associated with poorer psychological health (Hunt et al, 1999), fatigue (Hunt et al, 1999), sleep disturbance (Hunt et al, 1999), and, more recently increasing frailty (Wade et al, 2016). The measurement of pain is discussed further in Chapter 6.

2.3.5 Multisite pain over the life course

The number of reported pain sites appears to be stable over many years. Papageorgiou et al (2002) found that, once widespread pain is established, it is likely to persist, or recur, particularly if accompanied with somatic symptoms and older age (Papageorgiou et al, 2002). For example, Papageorgiou et al (2002) found, in their cohort of 1386 adults, that 77% of those aged 50 years and older who reported chronic widespread pain and had dry eyes, dry mouth and day time tiredness at baseline reported chronic widespread pain seven years later. The number of pain sites may be established in childhood; a UK study of 1,440 school

children found a widespread pain prevalence of 14.6% (Jones et al, 2003). The trajectory of multisite pain and all its associations may be therefore set early in life and any recommendations made in this thesis about the management of pain in relation to falls must consider that intervention to reduce pain early in the life course is important.

2.4 Pain in older people

2.4.1 Epidemiology of pain in the community

Prevalence estimates of pain in community-dwelling older people vary across studies according to sample size, estimation period and age group. A review of studies examining the prevalence of pain in older people reported the crude prevalence of any type of pain ranged from 0% to 93% (Abdulla et al, 2013). Nested within these pain prevalence estimates, multisite pain is a common complaint of older community dwelling adults with prevalence estimates ranging from 31% to 47% as outlined in table 2.1.

Table 2.1 The prevalence of multisite pain in community dwelling older adults

Study author (year)	Age (years)	n	Multisite pain %
Thomas et al (2004)	50 +	7878	47%
Stubbs et al (2015)	Mean age 77	295	31%
Levielle et al (2009)	70+	749	40%

Comparing the prevalence of multisite pain with other long-term conditions experienced in old age (whose primary care management is incentivised by the UK Government through the Quality and Outcomes Framework) demonstrates that multisite pain is more common than type 2 diabetes (prevalence between 13.3% and 26.2% in those aged 50 years and older (Diabetes UK, 2016)), cancer (prevalence in adults aged 65 years and older was 12.5% in 2010 (Maddams et al, 2012)) and chronic kidney disease (13.5% for people aged 65-74 and 32.7% for people aged 75 and over (Public Health England, 2011)) .

Evidence suggests that musculoskeletal diagnoses are the most common contributor to pain in older people. Mäntyselkä et al (2001) analysed 3417 primary care consultations for adults aged 40 years and older. Pain was a primary or secondary reason for visiting in 42% of analysed consultations and musculoskeletal diseases were the most common diagnoses (41% of those with pain) made during these pain-related consultations (Mäntyselkä et al, 2001).

There is a similar picture in UK primary care, where 1 in 3 adults aged 65 years and older visit their GP at least once over a 12 month period for any musculoskeletal pain (Jordan et al, 2010). Furthermore, Jordan et al (2010)

found, in their analysis of general practice records, that consultation rates for multisite musculoskeletal pain increased with age in men, accounting for 887 consultations per 10,000 registered men aged 75 years and older; consultation rates were much higher in women, at 1049 per 10,000 registered population aged 45-64 years, peaking at 1388 per 10,000 registered population between ages 65 and 74, and falling slightly to 1370 per 10,000 registered women aged 75 years and older.

The existing evidence suggests that multisite pain is a common occurrence in older adults, it is most likely to be caused by, at least in part, underlying musculoskeletal conditions, and that it is responsible for a high number of primary care consultations.

2.4.2 Impact of multisite pain in older adults

Not only is multisite pain a common complaint in older people that generates multiple primary care visits, evidence is emerging to indicate multisite pain as an entity is associated with detrimental health and wellbeing experiences.

For example, Westoby et al (2009) demonstrated a statistically significant association between pain lasting longer than 4 weeks and reporting a subjective cognitive complaint. Older adults who reported pain also reported a greater degree of cognitive complaint in a dose-response relationship; this relationship also held when the pain groups were divided into no pain and widespread pain groups.

More recently, multisite pain has been associated with poorer health-related quality of life, with increasing number of pain sites statistically significantly associated with reduced quality of life scores on the Short Form-12 survey (Lacey et al, 2014). Again, this relationship followed a dose-response pattern with increasing number of pain sites linked with deteriorating quality of life scores (Lacey et al, 2014).

Data from a UK population-based cohort study, the English Longitudinal Study of Ageing, were used at two time points to measure the association between pain and subsequent development of frailty. 5,316 men and women responded to the surveys and those reporting moderate or severe pain were significantly more likely to be frail at follow up (Wade et al, 2017). This relationship also held when analysing chronic widespread pain. In a different study population of 2,736 European men aged 40-79 years, those reporting chronic widespread pain at baseline were statistically significantly more likely to develop frailty 4 years later with a 70% higher frailty index at follow up compared to their pain-free counterparts (Wade et al, 2016).

2.5 The place of general practice in managing pain

Multisite pain is a common experience in older people; it generates a high number of general practice consultations and is associated with detrimental consequences for patients, families and the wider community. Understanding the role of general practice in managing multisite pain provides the context in which results will be placed to ensure useful, practical recommendations are made to general practice clinicians and policy makers.

General practice is a cornerstone of healthcare systems around the world. It is usually the point of first medical contact within a health care system and deals with all health problems regardless of age, sex or other personal characteristics (European Academy of Teachers in General Practice, 2011). It is further defined by the efficient use of health care resources by coordinating care with other professionals in primary and secondary care and the promotion of health and well-being through 'appropriate and effective intervention' (European Academy of Teachers in General Practice, 2011).

General practice involves a holistic approach in understanding and respecting values, culture and family beliefs and the way in which these affect the experience and management of health and sickness (General Medical Council & Royal College of General Practitioners, 2013). Considering pain as a biological, psychological and social entity, general practitioners and other healthcare practitioners working in general practice are therefore ideally placed to manage multisite pain.

2.6 Summary

This chapter has defined pain and placed it within a general practice context. Pain is a common life experience across the age spectrum and multisite pain is associated with poor outcomes including health-related physical functioning, work-related disability, cognitive complaint and frailty. The next chapters will explore the epidemiology of falls in older people, the current evidence around falls prevention and emerging evidence that multisite pain is associated with an increased risk of falls.

Chapter 3: Falls

3.1 Introduction: why research falls in older people?

Falls are a significant problem for older people, their families and communities, for health and social care services and for the UK economy. Falls are common, become more frequent with advancing age and frailty, and have serious consequences. As the UK population ages, falls will become an even greater burden and the need to mitigate this is pressing. This chapter outlines the size of the problem, first by introducing the concept of population ageing and frailty, then describing the prevalence, severity and consequences of falls in older people. A definition of falls is put forward and a chapter summary is provided.

3.2 The ageing population

The world's population of older people is increasing. The World Health Organisation (2012) predicts that between 2000 and 2050 the global population's proportion of adults aged 60 years and over will double, from 11% to 22% (World Health Organisation, 2012). In the UK, the number of people aged 65 years and over is expected to rise from 10.3 million in 2010 to 16.9 million in 2035. The number of people aged 80 years and over is expected to rise from 2.9 million in 2010 to almost 5.9 million in 2035 (Office for National Statistics, 2012).

Since the annual costs of health and social care are significantly greater for older people (The Kings Fund, 2017), the ageing population may well increase overall health and social care spending, particularly for problems associated with older people, for example increasing frailty and falls. Alternatively, if older people

remain well in advancing age, their continued contribution to society through paid work, spending power, volunteering and donations will be possible and there may be additional benefits to the economy (The Kings Fund, 2017).

Therefore, as the population ages and health problems associated with ageing increase, exploring ways to reduce falls and their consequences is necessary to ensure people remain well through their advancing years.

3.3 Frailty, aging and falls

Frailty is a defined as “a state of vulnerability to poor resolution of homeostasis after a stressor event” (Clegg et al, 2014). Frailty is a consequence of age-related decline in many physiological systems including musculoskeletal, cardio-respiratory, renal, endocrine and neurological systems (Clegg et al, 2014). This means that recovery from stressor events including falls is more difficult with increasing frailty and advancing age as physiological systems have reduced capacity to recover to previous levels of functioning. Frailty therefore has a significant impact on the ability of older people to recover from falls.

3.4 Defining falls

The internationally recognised definition of a fall, proposed by the Prevention of Falls Network Europe (ProFaNE) group is “an unexpected event in which the participants come to rest on the ground, floor, or lower level” (Todd & Skelton, 2004).

There are many different definitions of falls used in the literature although most are based upon the gold standard definition from ProFaNE, for example the National Institute for Health and Care Excellence’s (NICE) definition in the Falls Prevention guideline: “an unintentional or unexpected loss of balance resulting in coming to

rest on the floor, the ground, or an object below knee level" (National Institute for Health and Care Excellence, 2013).

The ProFaNE definition makes sense from clinical and research perspectives; it is general enough to ensure that multiple aetiologies are accounted for (for example, collapse due to postural hypotension and loss of balance due to medication side effects) and ensures that vague terms including 'stumble' or 'trip' are classified as falls if they result in coming to rest on the ground, floor or lower level.

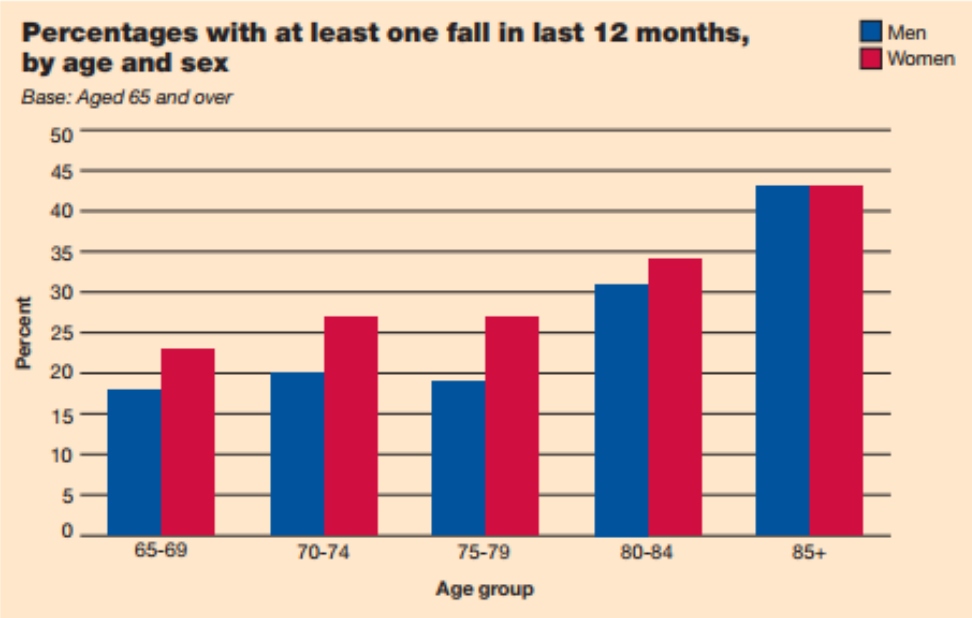
The lay definition of fall is more problematic as the concept of 'being a faller' is surrounded by negativity, for example the stigma of 'becoming old and frail' (Age UK, 2017). For example, an older person who stumbles backwards onto a chair or bed might not consider themselves as a faller for fear of the consequences of being labelled as 'frail'. This may result in misclassification bias as subjects are reluctant to classify themselves as fallers and thus impact upon research findings.

3.5 Falls prevalence in older people

Falls are common in older people and prevalence increases with age. In 2005, the cross-sectional Health Survey of England surveyed 4259 adults aged 65 years and older living in private households. 29% of women and 23% of men reported at least one fall in the previous 12 months and falls prevalence increased with age in men and women, with approximately 42% of adults aged 85 years and older reporting one or more falls in the preceding 12 months, as demonstrated in Figure 3.1 (National Statistics and NHS Information Centre, 2007).

Another cross-sectional UK study, the English Longitudinal Study of Ageing, surveyed 4352 adults aged 60 years and older and found that falls prevalence increased from 20.8% in those aged 60-69 years, through 27.7% for those aged 70-79 years to 33.2% for those aged 80 years and older (Gale et al, 2016).

Figure 3.1 Prevalence of falls in older people



A smaller cohort of UK-based community-dwelling adults aged 90 years and older (90 women and 20 men) were followed over a 12 month period; 58% were reported to have fallen at least once in the previous year and 60% reported at least one fall in the prospective 12 month follow-up (Fleming et al, 2008). These UK-based studies of community-dwelling older people all demonstrate the same trend, that falls are common, even amongst the youngest old, and falls increase in prevalence with advancing age.

This picture is reproduced globally, for example Dore et al (2015) undertook a cross-sectional survey of 1,619 community-dwelling adults with a mean age of 62 years old and found approximately 20% reported a fall in the preceding 12 months (Dore 2015). A cross-sectional survey of 2,096 community-dwelling adults aged 65 years and older in Nigeria found that 24% of women and 18% of men reported a fall in the previous 12 months (Bekibele & Gureje, 2010). In Japan, a survey of 1,351 community dwelling adults aged 65-74 years found that 19% had fallen in the past year (Harada et al, 2015); this figure is lower than the prevalence quoted in other studies, perhaps due to a younger sample and only those without physical activity restriction being selected. Falls are therefore common in older people worldwide.

Comparing prevalence of other common chronic diseases in the UK provides a reference for the prevalence of falls. For example, as presented in Chapter 2, the comparatively low prevalence of diabetes mellitus (13.3-26.2% (Diabetes UK, 2016) and cancer (12.5% (Maddams et al, 2012) demonstrate that falls are a common and important problem in older people.

3.6 Fall severity

There is a spectrum of fall severity, ranging from falls that require no medical assistance to falls that result in serious injury, hospital admission and death. This categorisation of falls relies on healthcare seeking behaviour, an activity that can be measured with routinely collected healthcare data. Of course, 'no healthcare assistance sought' does not necessarily equate to 'no healthcare assistance required', and many people will turn to lay resources for help including family, friends and charities.

3.7 Consequences of falls

Any type of fall within the falls 'severity' categorised according to healthcare needs has significant consequences for individuals, their families and wider society, whether it is a fall that does not require healthcare assessment or a fall that results in a prolonged hospital admission. An arbitrary categorisation of the biological, psychological and social consequences of falls is useful to present evidence, although these are not mutually exclusive entities.

3.7.1 Biological consequences

The biological consequences of falls, including fractures and death, increase towards the tip of the falls pyramid. Falls are the most common cause of accidental injury and accidental death in adults aged 75 years and older (British Geriatrics Society, 2007, Scuffham & Chaplin, 2002).

A systematic review of falls resulting in injury (termed injurious falls) reporting (Schwenk et al, 2012) found the proportion of injurious falls to all falls ranged from 3.6 % to 63.5%, with studies using only fracture outcomes finding the lowest proportion and studies using a broader definition of injury including bruises, cuts and abrasions reporting the highest proportion of injuries in relation to all falls (Schwenk et al, 2012). In the UK, this equates to 65,000 hip fractures occurring each year (Royal College of Physicians, 2015). Of these hip fractures, the UK Department of Health report that up to 14,000 people die annually in the UK (Department of Health, 2001).

Falls have a considerable impact on everyday clinical management of common medical conditions in general practice. For example, part of the management of

future falls risk involves medication modification or withdrawal (National Institute for Health and Care Excellence, 2013). In practice this may mean stopping medication that is benefitting other symptoms to reduce the risk of falls, for example benzodiazepines that provide relief from anxiety and insomnia or gliclazide that improves glycaemic control in diabetes mellitus. Although the falls risk is reduced, the impact of withdrawing medication previously of benefit must be carefully weighed to assess impact on all aspects of patients' daily lives, including the biological aspects of other diseases. The biological consequences of falls are wide ranging and considerable, particularly as falls severity increases.

3.7.2 Psychological consequences

The psychological consequences of falling can be severe across the falls iceberg; even a fall that does not require healthcare assistance is enough to induce a fear of falling. Fear of falling is a recognised risk factor for future falls (National Institute for Health and Care Excellence, 2013) and is common amongst older adults who have fallen or nearly fallen with up to 85% of older community dwelling adults reporting a fear of falling (Scheffer et al, 2008). Loss of self-efficacy (defined as an individual's perception of capabilities within a particular domain of activities (Bandura, 1977)), activity avoidance and loss of self-confidence are other psychological sequelae of falls (Legters et al, 2002).

Loss of independence associated with falling is a significant concern for older people; a survey of older women found that 80% would rather be dead than experience the loss of independence and quality of life resulting from a hip fracture and subsequent nursing home admission (Salkeld et al, 2000). Older people fearing loss of independence from any fall, even those not requiring healthcare assistance, do so for good reason; for a home-visiting GP, safety at home is a key

consideration and if an older person is considered to be at high risk of falling (and a history of falls or near-falls forms part of this risk assessment) and thus not safe at home, then an emergency social care admission is often advised and arranged and personal independence is inevitably compromised.

3.7.3 Social consequences

The activity avoidance and loss of confidence arising from experiencing a fall has a significant impact upon social participation amongst older people and impacts upon individuals, families and communities. The grandmother who has stopped attending the local community centre to help out at coffee mornings because the steps on the bus are too difficult to negotiate, or the retired clockmaker who has stopped helping at local 'fix it' events because the ground is too uneven outside the host building are just two examples of decisions that older people are making on a daily basis due to their fear of falling and reduced confidence; actions which result in losses to all involved.

Furthermore, there is evidence that reduced social participation in older adults is associated with poorer mental health (Thraen-Borowski et al. 2013), greater cardiovascular risk (Kamiya et al, 2010) and increased mortality (Glass et al, 1999, Dale et al, 2012). Reduced social participation therefore has far-reaching consequences.

An increase in social support and care is often required after a fall if help is needed with activities of daily living, for example washing, dressing, preparing meals and shopping. This help can be provided by formal social care structures, for example residential homes and caring services or by family, friends or neighbours. The Kings Fund (2013) analysed healthcare data in a cohort of older

people in Torbay, UK by costing care in the 12 months preceding and 12 months immediately following a fall (Tian et al, 2013). This study found both community care costs (community hospital inpatient and community health visits) and social care costs (domiciliary care, day care and care homes) increased after a fall (GP services and prescriptions were not included in the analysis) (Tian et al, 2013). Moreover, Pin & Spini (2016) found that one fall event, regardless of physical consequences, independently predicted increased social support. This increased need has obvious consequences for families and communities including creating time for caring roles at the expense of other activities including work.

Falls therefore impact upon individuals, families, communities and local health and social care services through reduced social participation and increasing social support needs.

3.7.4 A note on 'injurious' falls

The term 'injurious' is commonly seen in the literature addressing falls. 'Injurious' is defined as 'causing damage or harm; deleterious; hurtful' (Collins English Dictionary, 2016). Hence, a fall that results in a deleterious effect can be described as 'injurious'. As outlined in Section 3.7, the consequences of falls are far-ranging and can arise from a fall of any severity. This thesis therefore avoids using the term 'injurious' fall and will classify falls according to healthcare use.

3.8 Economic consequences of falls in older people

Falls have an economic impact upon health and social care services. The English Longitudinal Study of Ageing found 28.4% of adults aged 60 years and older experienced a fall that did not require healthcare attendance (Gale et al, 2016).

There is little data available on the number of primary care attendances due to falls. Gribbin et al (2009) used The Health Improvement Network (THIN) database of GP consultations to research falls and medication use finding 79,295 recorded fall events in 61,248 individuals over 3 years.

It is difficult to tease out the proportion of older adults who experience a fall that requires Emergency Department attendance or hospital admission since these figures are generally quoted as numbers of falls, rather than number of fallers. Number of falls remains a useful estimate of the impact on healthcare services as fallers will need to undergo similar resource use whether they are a new or recurrent faller. Accordingly, there were 647,721 A&E attendances for fall-related injuries in adults aged 60 years and older in 1999 (Scuffham & Chaplin, 2003). These A&E attendances generated 204,424 admissions to hospital due to fall-related injuries (Scuffham & Chaplin, 2003). Although these figures are from 1999, they are unlikely to have reduced significantly and may have risen due to the effect of an ageing population.

More recent metrics on falls that required hospital admission come from the Torbay Cohort (Tian et al, 2013) who identified fallers requiring hospital admission from hospital and GP data and analysed associated health and social care costs (Tian et al, 2013). Around 1% of the study population (adults aged 65 years and older living in the community) were admitted to hospital due to falls between July and December 2010.

Falls have recently been estimated to cost the NHS £2.3 billion per year (National Institute for Health and Care Excellence, 2017), from approximately £116 billion total NHS spend in the same year (The Kings Fund, 2017). This compares to a

total annual cost of £1.4 billion to manage diabetes mellitus and its complications (Diabetes UK, 2012) and £5 billion per year to treat cancer (Department of Health, 2015).

The numbers quoted above, although not directly comparable, provide a snapshot of healthcare utilisation and associated costs and demonstrate that falls in older people require substantial healthcare resources in the UK.

3.9 Summary

This chapter has defined falls, highlighted their prevalence, associated healthcare use and consequences and thus provided the reasoning behind studying falls in this thesis. The next chapter explores risk factors for falls and places this information in a clinical context through outlining the role of general practice in falls prevention for older people.

Chapter 4: Risk factors for falls

4.1 Chapter overview

This chapter provides an overview of the risk factors for falls in older people, derived from current clinical guidelines relating to the prevention of falls and from personal clinical experience. Research establishing an association between pain and falls is discussed to provide a foundation for this thesis' development. The chapter is then summarised.

4.2 Falls risk factors: review of current evidence

4.2.1 Overview

Many risk factors for falls have been identified in the literature. This section presents a description of the key evidence behind traditional risk factors that are commonly cited in clinical guidelines and highlights other risk factors that are not as widely recognised in clinical practice but are important to consider in the context of this thesis. Where relevant, the associations with pain are also discussed to provide a more clinically representative 'real-life' hypothesis of how the risk factor might interact with pain to impact upon falls risk.

The purpose of this section is to synthesise key information from current evidence that is later drawn upon in the thesis to decide which covariates are important to include in analyses with pain and falls; it is not intended to reproduce published literature reviews nor provide a comprehensive systematic review of falls risk factors as this work has already been undertaken, for example by Gillespie et al

(2012) who conducted and continue to update the Cochrane systematic review of interventions for preventing falls in older people living in the community.

The direction of this chapter was steered by personal clinical experience in assessing and managing older people who are at risk of falls or have already fallen within a primary care setting. Knowledge of current falls prevention guidelines (for example the NICE (2013) guidance on falls prevention) provided the starting point for literature exploration to examine the evidence behind falls risk factors within these guidelines. Experience of current daily clinical practice in primary care, falls prevention clinics and local GP educational events led to further literature searches to assess the evidence around additional factors that made clinical sense and seemed to be more common in patients who fell, for example hearing impairment, health anxiety, low mood. What now follows is a description of proven or possible falls risk factors that are considered for inclusion in this thesis' analyses.

4.2.2 Risk factors: demographic information

4.2.2.1 Age

Increasing age is a known risk factor for falls, a finding that has been reproduced by many studies through the years. In addition to the evidence presented in Chapter 3, Blyth et al (2007) found that, in a population of community-dwelling older adults, the relative risk of falls in the past 12 months increases with advancing age. Using the age group 40-59 years as the comparator group, Blyth et al (2007) reported a non-statistically significant increased relative risk of 1.09 (95% confidence interval 0.94-1.25) in those aged 60-69 years, a statistically

significantly increased relative risk of 1.74 (95% confidence interval 1.48-2.05) for those aged 70-79 years and a statistically significant increased relative risk of 1.37 (95% confidence interval 1.23-1.53) for those aged 80 years and older. Barrett-Connor et al (2009) found that women aged 80 years and older had a statistically significant odds ratio of falling equal to 1.53 when compared with women aged 50-69 years old and Deandrea et al (2010) found that, for every 5 year increase in age, the odds of falling increased by 12%, a statistically significant finding.

4.2.2.2 Sex

Studies exploring falls risk factors give conflicting results for the influence of sex on falls risk. For example, Campbell et al (1990) found no difference in fall rate between females and males in their community based prospective study of 761 older adults. However, Blyth et al (2007) found that the relative risk of females falling over the past 12 months compared to males was 1.37, a statistically significant finding in their sample of 3181 subjects aged 49 years and older. Gale et al (2016) analysed their results in a different way, grouping subjects by sex, and then by age, using the youngest age group as the baseline risk of falls. Men and women were both more likely to fall with increasing age, although the risk of falls with advancing age was more pronounced in men; this is likely to be because women overall fell more frequently and so the baseline risk was higher (at ages 60-69 years, 20.8% of men and 26.6% of women fell in the last two years, and this increased at ages 70-79 with 27.7% of men and 30.5% of women falling and again at ages 80 years and older with 33.2% of men and 35.1% of women falling) (Gale et al, 2016). Although there is some discrepancy over the exact relationship between falls and sex at different ages, sex does impact upon the risk of falls.

4.2.2.3 Ethnicity

Few studies have explored the influence of ethnicity on falls risk. Nevitt et al (1989) found that caucasians were more likely to fall than their afro-caribbean, hispanic or south asian counterparts and Friedman et al (2002) confirmed this finding as part of an exploratory study for falls risk factors. More recently, Geng et al (2017) conducted an analysis to specifically measure the influence of ethnicity on falls risk using cross-sectional study data from 6277 women aged 65 – 90 years old. They found that 28.5% of non-hispanic white women, 27.8% hispanic women, 23.4% black and 20.1% asian women had fallen in the past year, with asian and black women significantly less likely to fall when compared to white women (Geng et al 2017).

4.2.2.4 Socio-economic position

Socio-economic position refers to the socially derived economic factors that influence what positions individuals or groups hold within the multiple-stratified structure of a society (Galobardes et al 2007). There is evidence that socioeconomic factors influence health and as such the relationship between socio-economic status, pain and falls is likely to be complex. Barnett et al (2012) undertook a large cross-sectional study extracting medical record data from 1,751,841 patients in Scotland and found that multimorbidity is likely to begin 10 to 15 years earlier in people living in the most deprived areas compared with the most affluent. Furthermore, those in socio-economic deprivation were found to be much more likely to have pain disorders and mental health disorders as comorbidities (Barnett et al, 2012). These findings from a large scale study

suggest that the influence of socio-economic status on health and comorbidity is complex and one that must be considered in this thesis since this might also subsequently impact upon risk of falls. For example, if respondents reporting pain are more likely to be from deprived socio-economic groups, then the pain groups will have an unequal distribution of socio-economic statuses i.e. the pain-free group will have proportionally less individuals from lower socio-economic categories than the some pain or widespread pain groups. This means that differences in falls rates might be explained by socio-economic status rather than pain status, or that socio-economic status is acting as a confounder in the relationship between pain and falls. Furthermore, those in more deprived socio-economic groups may have more multimorbidity at a younger age. Thus any relationship between pain and falls within different age groups may be (at least partly) explained by the difference in multimorbidity patterns due to socio-economic status.

4.2.3 Risk factors: Physical health factors

4.2.3.1 Multimorbidity

Many medical conditions have been identified as risk factors for falls including circulatory disease, chronic obstructive pulmonary disease, depression and arthritis (Lawler et al, 2003). Loss of peripheral sensation as a result of diabetes (Luukinen et al, 1995) or arthritis (Nevitt et al, 1989) may increase the risk of falls. Urinary incontinence is a common finding amongst populations of older fallers (American Geriatrics Society et al, 2001); perhaps this is as a part of general

frailty, or due to the urgency required to attend to toileting needs which generates an additional risk associated with mobility problems and falls.

Compounding this, the burden of multiple chronic diseases has long been a known risk factor for falls, with Lawler et al (2003) finding the odds ratio for each additional chronic disease, when adjusted for the total number of medications, was 1.39 (1.29-1.51), a significantly increased risk of falls with increasing number of medical conditions. Deandrea et al (2010) also found the odds of falling per each additional comorbidity was statistically significantly increased (OR 1.2 (95% confidence interval (95% CI) 1.2-1.3)).

Multiple chronic medical conditions in an individual is termed ‘multimorbidity’ (Wallace et al, 2015) and this often results in polypharmacy (Wallace et al, 2015), a risk for falls in its own right which is discussed below. Marengoni et al (2011) conducted a systematic review exploring ageing with multimorbidity and found 22 studies reporting significant negative impacts of multimorbidity on disability, quality of life and high health care use (Marengoni et al, 2011). Four studies also found that increasing numbers of conditions were consistently associated with increasing risk of disability, although it is worth noting one study reporting a contrary finding of no relationship between multimorbidity and physical functioning (Hudon et al, 2008). Multimorbidity is therefore a risk factor for falls which may be driven by the associated polypharmacy and the impact of chronic disease burden upon physical functioning and resulting disability and thus increased risk of falls; a clinical picture that is common in daily general practice.

4.2.3.2 Dizziness

Many different interpretations are inferred from the use of descriptive terms such as ‘dizziness’ and ‘unsteadiness’. Dizziness may describe a sensation of light-headedness, for example due to postural hypotension or a vasovagal episode. Unsteadiness may describe symptoms relating to the inner ear or cerebellum. Balance and gait impairment may be due to central or peripheral causes. The wide differential diagnosis of underlying causes of these symptoms therefore makes it difficult to use particular diagnoses as indicators of ‘dizziness’. Taken as a symptom, dizziness, or unsteadiness, is a long established falls risk factor, demonstrated by Tinetti et al (1988) in her study of falls risk factors in older people. Tinetti et al (1988) found that the presence of ‘more than six balance and gait abnormalities’ (of unsteady sitting down, unable to stand on one leg unsupported, unsteady turning, unsteady after a gentle push on the sternum, increased trunk sway, unable to pick up walking pace, increased path deviation)’ had an OR for falls of 1.9 (95% CI 1.0 – 3.7). Dizziness has since appeared in national and international fall-related guidelines around the world for example NICE (2013) and American Geriatric Society guidelines (2001).

4.2.3.3 Hearing impairment

A recent systematic review and meta-analysis exploring the relationship between hearing loss and falls in older adults identified 12 studies and reported a pooled odds ratio of 2.39 (95% confidence interval 2.11-2.68) (although it must be noted that the studies included were predominantly cross-sectional and thus a temporal relationship was not possible to ascertain (Jiam et al, 2016)). Given this association and biological explanations including possible co-existent vestibular

dysfunction and resulting unsteadiness, the increased cognitive requirements of hearing loss reducing overall additional capacity for tasks including balance (Jiam et al, 2016) and the potential loss of special awareness (Keller et al, 1999), it is necessary to consider the influence of hearing on falls risk during analyses.

4.2.3.4 Visual defects

Reduced visual functioning is a well-established risk factor for falls with potential mechanisms for falls resulting from visual impairment relating to inability to see obstacles, reduced spatial awareness and reduced cognitive capacity for balance with the increased load of visual impairment. The Blue Mountain Eye Study conducted by Ivers et al (1998) found a statistically significant increase in risk of two or more falls with having reduced visual impairment. Subsequent research confirms this finding (Abdelhafiz & Austin, 2003; Patino et al, 2010), and visual impairment routinely forms part of the falls prevention agenda with organisations including the British Geriatrics Society and the College of Optometrists leading a national programme in eye health to reduce falls in older people (British Geriatric Society & British College of Optometry, 2010) .

4.2.3.5 BMI

A low body mass index (BMI) has been traditionally considered a risk factor for falls due to associated sarcopaenia and resulting muscle weakness and balance problems. Tinetti et al (1995) found that low body mass index was a risk factor for falls (OR 1.8, 95% CI 1.2-2.5) in her study of 1103 community dwelling older people. More recently, a high body mass index has been found to contribute to

falls risk. Hooker et al (2016) prospectively studied 5,834 older men and found that obesity (defined as BMI of 35 or more) was independently associated with statistically and clinically significantly higher fall rates (Hooker et al, 2016). This finding was later replicated in a Canadian study by Handrigan et al (2017) who found in their 15,860 sample of older community dwelling adults that there was a significantly higher odds of falling in obese men compared to normal weight (BMI between 20-25) men. This relationship did not exist for women. Furthermore, men classified as 'underweight' (BMI less than 20) had more falls than their 'normal' counterparts, although this was not a significant association (Handrigan et al, 2017). Since there are significant associations between BMI and falls it is prudent to account for this in analyses to ensure that any association between pain and falls is less likely to be attributed to BMI.

4.2.4 Risk factors: mental health markers

4.2.4.1 Cognitive impairment

Cognitive impairment is an established risk factor for falls and features widely in national guidelines. A recent systematic review and meta-analysis exploring the association between cognitive impairment and falls found that cognitive impairment as a disease-specific diagnosis (for example Alzheimer's disease) conferred a statistically significant risk of falls, although the evidence relating to other measures of global cognitive impairment (for example the Mini Mental State Examination) showed mixed findings, perhaps due to the high risk of bias or the subtleties of cognitive impairment that are not scored as such in the assessment tool (Muir et al, 2012).

Subjective cognitive impairment has been shown to be significantly associated with the presence of pain in older people (Westoby & Mallen 2009) and it is biologically plausible that cognitive impairment appears on the pathway between the experience of pain and subsequent falls; thus cognitive impairment is an important risk factor for falls.

4.2.4.2 Depression

A recent prospective study by Hoffman et al (2017) demonstrated a statistically significant association between the reporting of depressive symptoms and subsequent falls risk when controlled for baseline physical functioning, vision, chronic conditions, social support and neighbourhood social cohesion (Hoffman et al, 2017). Although this significance was lost when use of psychiatric medicines was added to the model, the importance of the relationship between depressive symptoms and falls remains since psychiatric medication would not be necessary if depressive symptoms did not exist.

An earlier study by Antsey et al (2008) demonstrated that, over 8 year follow up, the relationship between depressive symptoms and subsequent falls remained significant when controlled for sociodemographics, psychotropic medication, comorbidity and sensorimotor function.

It is known that older adults who report musculoskeletal pain are more likely to have comorbid depressive symptoms (Mallen et al, 2008). It is therefore important to take account of these symptoms since it may be that the relationship between pain and depression is exerting an influence on the association between pain and falls.

4.2.4.3 Anxiety

The relationship between anxiety symptoms and falls risk has been less extensively investigated than depressive symptoms and falls risk. The first study available in the literature specifically designed to explore the relationship between anxiety and falls was published in 2016. Holloway et al (2016) found that anxiety was associated with an almost three-fold increased risk of future falls in older men. The increased risk in older women was subsequently explained by psychotrophic medication use, poor mobility and socioeconomic status (Holloway et al, 2016). Jones et al (2010) found those who do not report musculoskeletal pain had low levels of anxiety (and also low levels of depression and psychological distress), leading to the hypothesis that those reporting high levels of musculoskeletal pain would also report higher levels of anxiety. It is plausible that anxiety may act as a confounder in the same manner as depression might as cited in section 4.2.4.2; thus it is important to consider the presence of anxiety symptoms in analyses.

4.2.5 Risk factors: medication

4.2.5.1 Total medication count

In 2009, a meta-analysis of the impact of 9 medication classes on falls in older people demonstrated use of sedatives, neuroleptics, antipsychotics, hypnotics, antidepressants, benzodiazepines and non-steroidal anti-inflammatory drugs (NSAIDs) showed a significant association with falls (Woolcott et al, 2009). There are many individual studies included in this review that found significant associations between medication use and falls, for example Lawlor et al (2003) who found an increased risk of falls associated with use of hypnotics, anxiolytics

and antidepressants when adjusted for chronic disease status in 3742 community dwelling older women in the UK. This study also found a 'strong linear association' between the total number of medications and subsequent fall, although this lost statistical significance when adjusted for chronic disease status, physiological parameters and socioeconomic position (Lawler et al, 2003). When the number of medications is analysed categorically, more than four medications (irrespective of type) has been shown to attribute a significant risk of falls, for example by Robbins et al (1989) The latest research to date addressing polypharmacy and falls found that, after adjusting for covariates, polypharmacy did not remain a significant risk factor for falls in older adults although consumption of two or more 'high risk' medications including cardiovascular agents, central nervous system drugs, analgesics and endocrine drugs remained a significant risk factor for falls (Zia et al, 2017). This paper categorised medications differently to other publications, for example classifying polypharmacy as '5 or more medications' and including endocrine medications as fall risk increasing drugs. Nevertheless, the message that multiple medications increase falls risk remains.

4.2.5.2 Analgesic use

Pain is associated with analgesic use, and analgesics, particularly opiates and NSAIDs have been associated with an increased risk of falls in older people (Zia et al, 2017). A prospective study including 4231 older people found that, for those with or at risk of knee osteoarthritis, use of opiates (and antidepressants) conferred an increased risk of future falls when adjusting for covariates (Lo-Ciganic et al, 2017). However, it must be noted that Leipzig et al (1999) did not

find a significant relationship between opiates or NSAIDs and falls in their systematic review and meta-analysis of analgesic drugs and risk of falls (Leipzig et al, 1999) and Woolcott did not find a significant association between narcotics and falls in older people in his meta-analysis of medication and falls risk (Woolcott et al, 2009). The relationship between analgesic use and future falls is important to consider in this thesis, since increased risk of falls from analgesic use mean recommendations for pain management using pharmacological means will be more challenging.

4.2.6 Risk factors: physical functioning

Impaired mobility results in a limitation of physical functioning, which in turn leads to more sedentary behaviour, loss of muscle power and thus an increased risk of falls (Todd & Skelton, 2004). The presence of pain is also associated with mobility limitation (Mottram et al, 2008; Landi et al, 2009). Thus, physical functioning and mobility limitation might conceivably influence the relationship between pain and falls; the group with the most pain will also have the highest levels of mobility limitation and therefore the increased risk of falls might then be attributed to physical functioning rather than the presence of pain.

4.2.7 Risk factors: previous history of falls

Nevitt et al (1989) found that a history of at least three previous falls or one fall resulting in injury was statistically significantly associated with future falls risk (the unadjusted relative risks were 2.2 (95% CI 1.70-3.0) and 2.6 (95% CI 1.6-4.4) respectively). Barrett-Connor et al (2009) analysed data from 66,134 post-

menopausal women in a large prospective cohort and found that, after adjusting for multiple variables, the strongest single predictor of future falls was a history of falls, with an odds ratio of 2.67 (2.56-2.79). A history of falls is therefore an important risk factor for falls in older people.

4.2.8 Risk factors: summary

There are multiple risk factors for falls, including demographic, medical, psychological and physical health-related variables. These risk factors are not mutually exclusive and combinations of variables further increase risk of falls. For example, Barrett-Connor et al (2009) found the risk of falling increased linearly with the number of risk factors present, increasing between 2% and 9% for each additional risk factor. This increased risk is obviously due to the addition of each individual risk factor but is also likely due to the complex relationships between variables. For example, an older person with two chronic diseases might be taking four different medications and the side effects of these medications might make them feel a bit dizzy so activity is limited for fear of falls. This person already has two clear risk factors in multimorbidity and polypharmacy; when dizziness, fear of falling and activity limitation are added the risk of falling increases further.

4.3 Multisite pain and falls

A further potential risk factor for falls was identified by Leveille et al in 2009. They proposed that, on the basis of their population based cohort study, multisite pain is associated with an increased risk of falls in older people. Alongside personal clinical interest in care of older people and falls and the frustration that, despite

guidelines, our older patients are still falling, Leveille's (2009) study proved the starting point for this thesis and will now be discussed in more detail.

4.3.1 Leveille et al, 2009: study design

In 2009, Leveille et al published the first population-based cohort study to establish a link between the presence of multisite pain and future falling. This section will outline the study design and findings. A thorough critical appraisal, performed as part of the systematic review and meta-analysis that follows in Chapter 5, found the overall risk of bias for the study to be low. 749 community-dwelling older adults residing in Boston (USA) completed baseline assessment and 18 monthly falls postcards, yielding a response rate of 53% (Leveille et al, 2009). Respondents were included if they were aged 70 years and older, were able to walk 20 feet without personal assistance, able to communicate in English, had sufficient vision to read the study material and were intending to stay in the area for two years (Leveille et al, 2009). Exclusion criteria were severe visual or hearing deficits and cognitive impairment scores suggestive of significant memory difficulties.

Recruitment took place over a 27 month period from 2005 and included sending letters to local community hubs and randomly selecting households within the locality to receive study information. A home interview and clinical examination were performed at baseline and 18 months, and monthly falls calendars (where respondents mark daily whether they have fallen or not) were completed throughout study duration. 76% of participants completed all 18 monthly calendars and more than 95% completed calendars at 6, 9, 12 and 18 month points.

The study focussed on ‘chronic musculoskeletal pain’ and therefore asked respondents about pain present in the previous year and present for at least three months in that previous year (Leveille et al, 2009). A thirteen item questionnaire was used to assess musculoskeletal pain in the hands, wrists, shoulders, back, chest, hips, knees and feet. Chest pain associated with angina was excluded. Pain was classified as i) no pain ii) single site pain ii) pain in two or more locations. A second set of pain location measures were defined according to pain site and followed the pattern: i) pain in the knee(s) and 1 or more other joint locations; ii) pain in the knee(s) only; and iii) no knee pain. Pain severity and pain interference were also measured. Finally, pain was also assessed monthly during study follow up using a single pain question designed to measure severity of pain over the past month; severity was recorded on the monthly falls calendars. The authors later refer to pain as ‘joint pain’ and present pain in more than one location as ‘polyarticular pain’.

The study also measured age, sex, ethnicity, education, cognitive status, physical activity, physician-diagnosed self-reported heart disease, stroke, Parkinson’s Disease, rheumatoid arthritis, spinal stenosis and spinal disc disease. Peripheral neuropathy, peripheral arterial disease, BMI, diabetes mellitus, osteoarthritis of the hand and knee, vision, standing balance and depression were assessed clinically. Information about medication, including over-the-counter medication was collected from recent prescriptions and questionnaires.

Falls were measured prospectively using a monthly falls calendar that participants completed daily and submitted monthly; this is the current gold standard of falls data collection in surveys, highlighted by the ProFaNE group (Hauer et al, 2006). Falls history in the 12 months prior to baseline survey was also ascertained.

4.3.2 Leveille et al, 2009: Study results

Leveille et al (2009) found that a fall in the past year was statistically significantly associated with the presence of pain, and the risk was greater amongst those reporting multisite pain compared to single site pain. Prospectively, the risk (rate ratio) of falls associated with single site pain was 1.19 (95% confidence interval (CI) 0.90 – 1.56) and, associated with multisite pain, was 1.70 (95% CI 1.34-2.16) when adjusted for age and sex. When adjusted for all the covariates outlined above, the final model demonstrated a rate ratio of falls of 1.11 (0.84-1.47) for single site pain and 1.53 (1.17-1.99) for multisite pain. Pain measured as severity or interference also statistically significantly increased the risk of future falls (Leveille et al, 2009).

4.4 Taking current research into pain and falls further

Leveille et al (2009) were the first group to provide evidence that pain in multiple locations is associated with an increased risk of falls. This thesis seeks to explore this relationship further in a larger study sample with a longer follow-up period in a UK-based community-dwelling population so that results can be interpreted with clinical relevance to UK general practice. Leveille et al (2009) also found that the increased falls risk persisted when controlled for factors that might be responsible for the cause of underlying joint pain, for example osteoarthritis, spinal disc disease and peripheral neuropathy; a finding that suggests there is something about the experience of pain itself that contributes to falls risk. This thesis seeks to further explore this relationship using the following different methods:

i) Using a broader definition of pain, including headaches and abdominal pain and thus not restricting to musculoskeletal, or joint, pain

ii) Taking account of a different set of covariates that are derived from current evidence around falls risk factors and from a pragmatic clinical stance

iii) Using different statistical techniques to explore self-reported falls and falls requiring primary or secondary health care utilisation

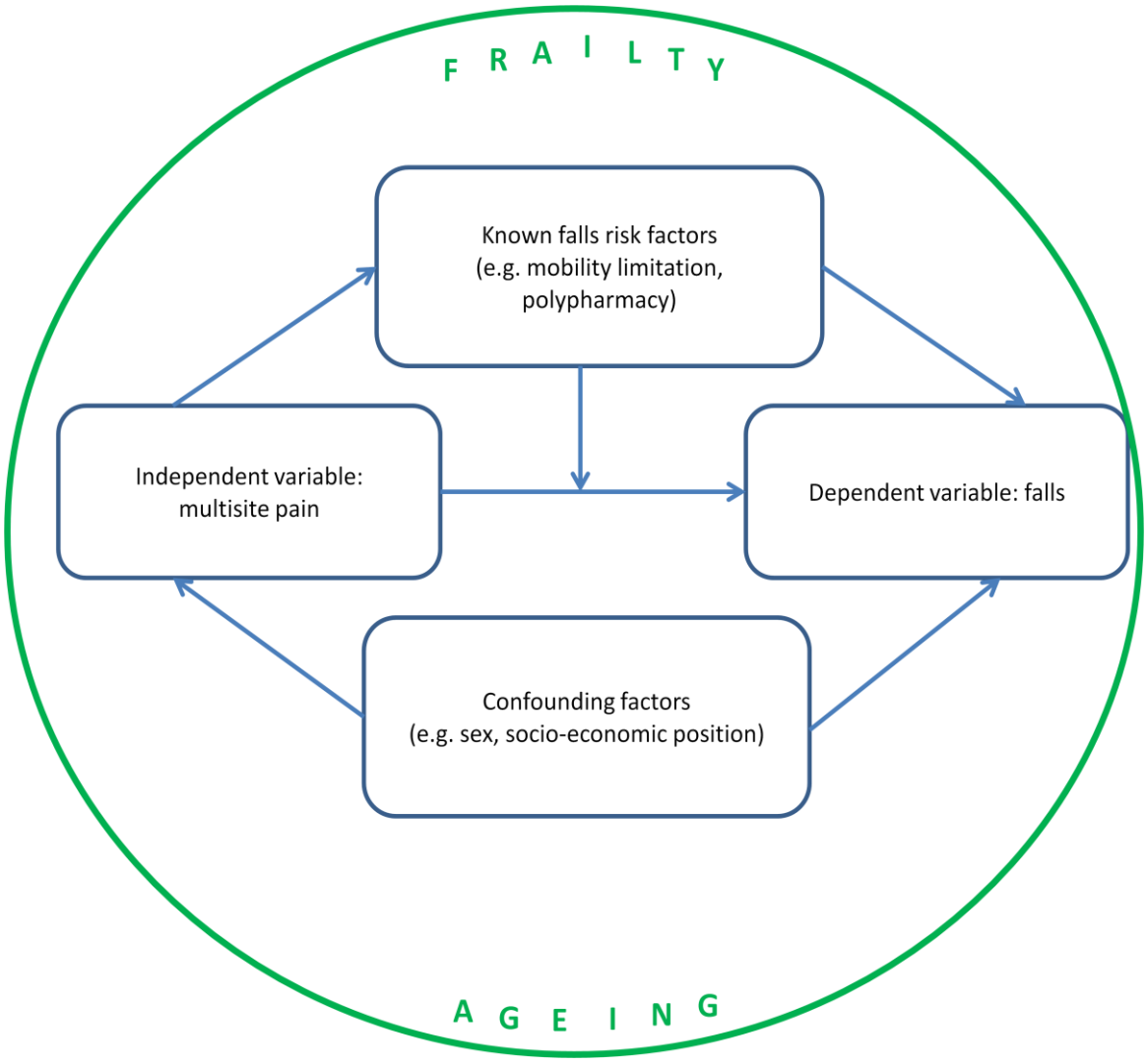
The next step in this thesis' development is to consider Leveille et al's (2009) research findings within the current evidence base examining the relationship between pain and falls. A systematic review and meta-analysis undertaken to address this next step is detailed in Chapter 5. The evidence presented in this chapter will be considered in conjunction with the findings of the systematic review and meta-analysis; selected covariates for inclusion in analysis are then described in Chapter 6.

4.5 A conceptual framework for the exploration of pain and falls

Finally, taking current research into pain and falls further must be done within the broader context of the themes discussed in the thesis in Chapters 2,3 and 4 in order to underpin and direct future analyses. Figure 4.1 presents a conceptual framework for the thesis in which the analysis is embedded within the broader context of frailty and population ageing. The thesis seeks to investigate the relationship between the independent variable (multisite pain) and the dependent variable (falls) whilst taking account of known falls risk factors and confounding variables and thus their potential influence on both the pathway between multisite

pain and falls and their influence upon the dependant and independent variables under investigation.

Figure 4.1 A conceptual framework for the thesis's exploration of multisite pain and falls in older people



4.6 Summary

This chapter has provided an overview of the known risk factors for falls in older people, derived from current clinical guidelines relating to the prevention of falls and from personal clinical experience. The first prospective cohort study to suggest a link between multisite pain and falls has been presented and the ways in which this thesis will build upon those findings have been outlined. Finally, a conceptual model has been presented to link together the broader themes underpinning the thesis and to aid future analyses. The next chapter considers additional evidence relating to pain and falls in a systematic review and meta-analysis.

Chapter 5: Multisite pain and falls: systematic review and meta-analysis

5.1 Overview

This chapter describes the process of the systematic review and meta-analysis undertaken to identify and synthesise the current evidence investigating pain as a risk factor for falls in older people. Results are presented and discussed, with the findings used to develop this thesis' research methodology.

5.2 Systematic review and meta-analysis: aims and objectives

5.2.1 The role of systematic reviews and meta-analysis

Previous chapters have discussed risk factors for falls, and have highlighted Leveille et al (2009)'s finding that pain is statistically significantly associated with falls (Leveille et al, 2009). Further exploration of the current medical literature is required to fully identify additional research examining the association between pain and falls to enable this thesis to build on existing evidence and identify potential novel areas for further investigation.

Further exploration of the literature will be undertaken using a systematic approach, guided by the widely recognised process of systematic reviewing. The Cochrane Collaboration defines systemic review as an approach that 'attempts to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question' (Higgins & Green, 2011a). Where possible, summary statistics from each study will be combined to

provide an overall summary risk estimate of the relationship between pain and falls; this will be done using meta-analysis, an established technique of combining results from individual studies to produce a more precise effect estimate in order to reduce uncertainty (Higgins & Green, 2011a).

5.2.2 Aims and objectives

The systematic review and meta-analysis will identify existing research examining the relationship between multisite pain and falls, appraise individual studies for quality and risk of bias, and synthesise results into an overall summary in order to meet the following objectives:

i) To establish whether there is an increased risk of falls in older adults who experience multisite pain; and
ii) To identify gaps in the current evidence base that will be used to inform the design of this thesis' research to examine the relationship between multisite pain and falls in greater detail.

5.3 Methods

5.3.1 Medical literature databases and additional searches

Seventeen online bibliographic databases were searched from inception until 30th September 2016. The full list of the databases searched is found in Appendix 1. The search included databases storing medical research (including Medline, EMBASE, The Cochrane Library), nursing and allied health research (including CiNAHL and the British Nursing Index), behavioural science and mental health related research (including PsychInfo), health management research (for example

the HMIC Health Management Information Consortium) and health economics information (including the Kings Fund).

Additional data sources that were searched include journal conference proceedings (through the Conference Proceedings Citation Index), the Electronic Thesis Online Service and relevant charity or society websites (for example Age UK, British Geriatric Society). References of relevant papers were hand-searched to ensure relevant research not extracted previously was captured. A complete list of resources searched is found in Appendix 1.

5.3.2 Search strategy

The search was designed to maintain broad terms to ensure adequate capture of all relevant studies. A pilot search strategy using focussed search terms failed to extract key papers and thus the search strategy described below was used. The search terms were limited to appear in title, abstract or keywords.

5.3.2.1 Search terminology: pain

The general term ‘pain’, either as a MeSH term ‘exploded’ (a method of broadening a search that is built into database search software) or as free text had to be used to ensure capture of relevant research after a pilot search using terms more specific to multisite pain (pain in more than one part of the body, extracted using the search term ‘mulit$ adj3 pain’) failed to capture key studies.

In addition to ‘pain’, other terms used to capture multisite pain included musculoskeletal diseases, osteoarthritis, arthralgia and specific pain phenotypes

for example pain(ful) hip, pain(ful) knee); each were either ‘exploded’ as MeSH terms or searched as ‘free text’.

5.3.2.2 Search terminology: falls

Fall-related terms varied across databases. MeSH terms searched and ‘exploded’ were: ‘Accidental falls’, ‘falls risk’, ‘falls risk assessment’ and ‘falling’. The free text term ‘fall*’ was used to cover fall, falls, falling, fallen, falls and faller. A complete list of search terminology is detailed in Appendix 2.

5.3.2.3 Search study design

Studies were not excluded on the basis of study design alone. The systematic review seeks to establish whether there is an increased risk of falls in adults who experience multisite pain compared to those who with no pain; cross-sectional, prospective and retrospective cohort studies, and case-control studies are therefore all included from the outset and the quality of the study and interpretation of the conclusions take account of study design.

5.3.2.4 Search term combination and search limits

Pain search terms were combined using the Boolean operator ‘or’ to generate an overall ‘pool’ of pain-related search terms. Fall search terms were also combined using the ‘or’ operator.

The two separate ‘pools’ of pain terms and fall terms were then combined using the Boolean operator ‘and’ to extract literature containing both pain and fall-related search terms in either the title, associated keywords, or abstract.

Searches were limited to human studies only; no other limitations were applied including language. Translators were found for Italian, French, German, Dutch, Spanish, Portuguese and Japanese articles. Google Translate (Google, 2013) was used to translate one paper written in South Korean. No papers were excluded on basis of language alone.

5.3.2.5 Inclusion and exclusion criteria

Studies were included in the review if all of the inclusion criteria were met:

i) Study population

The study population must be community dwelling adults aged 50 years and older. Where a study contains a wider age range that includes adults aged 50 years and older, they remain included and, where possible, data for sub-groups is extracted or authors are contacted for further information.

ii) Exposure of interest

Participants must have multisite pain i.e. pain in more than one part of the body.

iii) Comparator group

There must be a group with no pain to enable comparison.

iv) Outcome

There must be a measure of falls, either as a baseline covariate or as a study outcome.

Studies were excluded if one or more of the following criteria were met:

i) Study population

The study population resided in nursing homes or were hospital inpatients.

ii) Exposure of interest

The pain measure does not quantify the number of pain sites, or there is only one body part that is being examined (e.g. a study exclusively about the knee) and so multisite pain cannot be assumed.

iii) Further information on pain and/or falls data was not available

Some studies appeared to have collected information on number of pain sites or falls as part of a larger piece of work but the information was not specifically reported in the publication. In these instances, author's names and online activity relating to the study were searched for further information. Study authors were also contacted for further information. Where no further information was available (either unable to find contact details, no response from enquiry, or author unable to provide the data), studies were excluded.

5.3.2.6 Data collection

Data collection took place in five stages as outlined below. The study selectors at all stages were VW, the author of this thesis, and Dr Lorna Clarson (LC), an academic general practitioner.

i) Title screening

The broad search strategy extracted a large volume of titles, often unrelated to pain and falls. Where there was no doubt as to the study subject from the title, irrelevant titles were excluded. Where more information was required, titles were

carried forward to stage two. A pilot round of title screening involving 50 titles was initially undertaken to ensure consensus amongst the two screeners (VW & LC). Each title was screened individually by both reviewers and the decisions were discussed. Inter-rater reliability was 100% with no discrepancies between reviewers.

ii) Abstract screening

All abstracts were screened by VW and LC. Studies were included for full text review if there was a possibility that the manuscript might contain information on multisite pain and falls, or if the abstract was poor quality and more information was required in order to reject it. Each reviewer screened half of the abstracts, split according to database source. Due to referencing software instability, duplicates were not removed and so it is likely that a substantial number of references were screened twice.

iii) Full text screening

The articles requiring full-text review were divided between VW and LC. Disagreements between reviewers were resolved by consultation with a third reviewer (Dr John McBeth, PhD Supervisor and Deputy Director of the Arthritis Research UK Centre for Epidemiology). The articles were not blinded before they were reviewed since evidence shows that blinding reviewers to authors makes little difference to decision-making (Berlin,1997).

Authors from articles selected for full text review were contacted for further information under the following circumstances:

a) If the manuscript or related work contained variables relating to pain and falls that were not explicitly linked in the manuscript but could feasibly provide information about the MSP and falls relationship
b) If more details were required to aid decision to include study, for example the exact information about pain held by the authors

If the information were available, authors were requested to conduct further analyses using multisite pain as the independent variable and falls as the dependent variable.

5.4 Quality assessment

5.4.1 Quality assessment tool design: QUIPs

There are numerous tools available to assist in the critical appraisal of prognostic studies including the Quality in Prognostic Studies (QUIPS) assessment tool (Hayden et al, 2006), a validated and widely adopted measure used to assess bias in prognostic studies (Hayden et al, 2006). QUIPS is the tool of choice for The Cochrane Collaboration when reviewing prognostic factors (The Cochrane Collaboration, 2012) and is therefore used for this systematic review.

The QUIPS tool considers sources of potential bias within a framework of six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and analysis (Hayden et al, 2006). A version of the checklist provided by the Cochrane Collaboration (The Cochrane Collaboration, 2012) is used to appraise each study included in the review. Each question in each domain is assessed and recorded as 'yes, partial, no or unsure' and then a summary for each domain is recorded as

a risk of bias ‘high, moderate or low’. Accordingly, the information presented in Box 5.1 was extracted from each paper. An example of the scoring system is found in Figure 5.1.

Box 5.1 Information extracted from included studies

Country of study setting
Sample size
Participant characteristics
Recruitment details
Inclusion and exclusion criteria
Follow up duration
Response rate
Loss to follow up
Description and classification of multisite pain
Potential confounders
Fall definition
Falls measurement
Fall-related outcomes
Study conclusion

5.4.2 Quality assessment of studies

Quality assessment of all full text studies was undertaken independently and agreement on quality assessment score was reached with the second reviewer (LC) in 100% of cases.

5.5 Data extraction

Data extraction of the information listed in Box 5.1 was performed by VW and entered into a purpose-designed spreadsheet.

Figure 5.1 The QUIPS critical appraisal tool (The Cochrane Collaboration, 2012) used to appraisal full text studies included in this thesis' review

Domain	Item	Rating of reporting	Rating of Risk of Bias
1. Study participation			
a. Source of target population	The source population or population of interest is adequately described for key characteristics*	Yes / partial / no / unsure	
b. Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias		
c. Recruitment period	Period of recruitment is adequately described		
d. Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described		
e. Adequate study participation	There is adequate participation in the study by individuals**		
f. Baseline characteristics	The baseline study sample is adequately described for key characteristics*		
Summary: Study participation	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between prognostic factor outcome		High / Moderate / Low
2. Study Attrition			
a. Proportion of baseline sample available for analysis	Response rate is adequate	Yes / partial / no / unsure	
b. Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described		
c. Reasons and potential impact of subjects lost to follow up	Reasons for loss to follow-up are provided		
d. Outcome and prognostic factor information on those lost to follow up	i) Participants lost to follow up are adequately described for key characteristics*		
	ii) There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not		
Summary: Study Attrition	Loss to follow-up is not assocated with key characteristics sufficient to limit potential bias to the observed relationship between prognostic factor and outcome		High / Moderate / Low

3. Prognostic factor measurement			
a. Definition of prognostic factor	A clear definition or description of prognostic factor is provided	Yes / partial / no / unsure	
b. Valid and reliable measurement of prognostic factor	i) Method of prognostic factor measurement is adequately valid and reliable to limit misclassification bias		
	ii) Continuous variables are reported or appropriate cut-points are used		
c. Method and setting of prognostic factor measurement	The method and setting of measurement of prognostic factor is the same for all study participants		
d. Proportion of data on prognostic factor available for analysis	Adequate proportion of study sample has complete data for prognostic variable		
e. Method used for missing data	Appropriate methods of imputation are used for missing prognostic factor data		
Summary: Prognostic factor	Prognostic factor is adequately measured in study participants to sufficiently limit potential bias		High / Moderate / Low
4. Outcome measurement			
a. Definition of the outcome	A clear definition of outcome is provided, including duration of follow up and level and extent of the outcome construct	Yes / partial / no / unsure	
b. Valid and reliable measurement of the outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias		
c. Method and setting of outcome measurement	The method and setting of outcome measurement is the same for all study participants		
Summary: outcome measurement	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias		High / Moderate / Low

5. Study confounding			
a. Important confounders measured	All important confounders, including treatments, are measured***	Yes / partial / no / unsure	
b. Definition of the confounding factor	Clear definitions of the important confounders measured are provided		
c. Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable		
d. Method and setting of confounding measurement	Method and setting of confounding measurement are the same for all study participants		
e. Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data		
f. Appropriate accounting for confounding	i) Important potential confounders are accounted for in the study design		
	ii) Important potential confounders are accounted for in the analysis		
Summary: study confounding	Important potential cofounders are appropriately accounted for, limiting potential bias with respect to the relationship between prognostic factor and outcome		High / Moderate / Low
6. Statistical analysis reporting			
a. Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis	Yes / partial / no / unsure	
b. Model development strategy	i) The strategy for model building is appropriate and is based on a conceptual framework or model		
	ii) The selected statistical model is adequate for the design of the study		
c. Reporting of results	There is no selective reporting of results		
Statistical analysis and presentation summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results		High / Moderate / Low

5.6 Data analysis

Raw data was extracted from the manuscripts, or from author correspondence where applicable. Raw data and effect estimates were entered into a purpose-built spreadsheet. All effect estimates were standardised to odds ratios to enable comparison; in cases where relative risk or alternative risk estimates were presented the raw data was used to calculate odds ratios and 95% confidence intervals. Odds ratios and confidence intervals were logarithmically converted and then Stata Statistical Software Release 14 (StataCorp, 2015) was used for analysis using the *metan* command. Forest plots were generated to display the effect size and associated 95% confidence interval for each individual study and the overall pooled estimate is presented.

Unadjusted odds ratios were used in the first instance to ensure that the studies that required an odds ratio to be calculated are comparable to studies that provide an odds ratio.

An analysis using adjusted odds ratios was then conducted to test the summary effect estimate under conditions that are more representative of clinical practice, for example considering putative confounders including age, sex, comorbidities and medication use.

A third analysis using only prospective cohort studies was than undertaken to obtain a pooled effect estimate for the risk of pain and future falls.

Following critical appraisal and a thorough understanding of each study's population and methodologies, it was reasonable to assume that the different studies are estimating slightly different yet related effects of pain on falls; this requires a random-effects meta-analysis, the simplest of which is the DerSimonian

and Laird (D&L) method (Higgins & Green, 2011b). Pooled odds ratios were therefore calculated using the D&L method in Stata Statistical Software Release 14 (StataCorp, 2015).

5.6.1 Measuring heterogeneity

To assess the consistency between studies, forest plots are drawn to enable odds ratios and their confidence intervals to be compared. If there is poor overlap of the confidence intervals for each individual study this may indicate the presence of statistical heterogeneity (Higgins & Green, 2011c). A formal measure of this heterogeneity is the Chi-squared test, where a low p value provides evidence of heterogeneity i.e. that the variation in estimate effects are unlikely to be due to chance alone, although it must be noted that a non-significant result does not mean absence of heterogeneity.

Since the studies included in the meta-analysis have different clinical populations and employ different methodologies, it is reasonable to assume that heterogeneity exists. The question is therefore not whether heterogeneity exists or not, but rather how much of an impact the heterogeneity has upon the effect estimate (Higgins & Green, 2011c). I^2 is thus used to describe the degree of inconsistency between studies, i.e. the percentage of variability in the effect estimate that is due to heterogeneity rather than chance (Higgins & Green, 2011c). Thresholds for I^2 are 0-40% (might not be important), 30-60% (may represent moderate heterogeneity), 50-90% (may represent substantial heterogeneity) and 75-100% (there is considerable heterogeneity) (Higgins & Green, 2011c).

5.7 Assessment of publication bias

Publication bias arises when studies with statistically significant results are more likely to be published than those with statistically non-significant, or unfavourable, results (Easterbrook et al, 1991; Ahmed & Riley, 2012). Studies with significant results are more likely to lead to multiple publications and to be published in journals with high citation rates, and are hence more likely to be found and included in systematic reviews (Easterbrook et al, 1991; Sterne et al, 2001).

Publication bias can be measured using funnel plots to chart the size of the effect estimate (x axis) with a measure of the study size (y axis). Because larger studies provide a more precise estimate of the effect, their effect estimates are more similar between studies (notwithstanding the impact of bias in effect estimation) and cluster around the true effect size. Smaller studies will have a more widespread distribution of effect estimates and these will be spread along the bottom of the graph horizontally. Theoretically, if all studies that measured the same outcome were plotted, a symmetrical inverted funnel shape would occur with smaller studies spread across the bottom of the graph and clustering occurring as sample size increases further up the y axis. Funnel plots will therefore be generated to explore the potential impact of publication bias on the summary risk estimate.

Funnel plots rely on subjective interpretation of symmetry, and so a statistical measure of symmetry is preferable although tests for funnel plot asymmetry should generally only be used when there are at least 10 studies included in the meta-analysis (Sterne et al, 2011). Begg's and Egger's tests are traditionally used to test funnel plot asymmetry. Begg's test looks for correlation between the individual study estimates and meta-analysis weight, i.e. whether the study

estimate is related to the study size. (Begg & Mazumdar, 1994) and Egger's test looks at the relationship between effect size and its standard error (since standard errors are dependent on effect size) (Egger et al, 1997). A p value of <0.05 associated with Begg's or Egger's testing means that publication bias may significantly impact results.

5.8 Results

5.8.1 Study identification

The search yielded 44,223 articles. A substantial proportion of these titles were not specifically evaluating the relationship between pain and falls. The search strategy did not indicate whether falls or pain was the outcome measure. Therefore, many studies identified discussed the impact of falls causing pain and injuries. Furthermore, since no age limit was applied, many studies related to childhood accidents and falls with resulting pain. 3031 titles proceeded to abstract review. After excluding studies not meeting inclusion criteria and duplicates, 451 articles proceeded to full text review. Twenty studies were included in the qualitative appraisal and 18 were included in meta-analyses; Figure 5.2 presents the study flow chart.

Three authors responded to requests for further information to enable analyses to be conducted (Bebikele, 2010; Holt, 2011; Marshall, 2016 (whose request for further information in 2013 was included in her paper subsequently published in 2016 and now included in this review)) and studies to be included in the full text review.

Twenty studies were eligible for inclusion into the systematic review. Table 5.1 summaries key study characteristics. The studies cover all continents. North America and Japan contribute the greatest number of studies. There were no studies identified from South Asia.

5.8.2 Study purpose

Eight studies set out in their primary objectives to investigate the association between the number of pain sites and falls (Asai et al, 2015; Kitayuguchi et al, 2015; Kitayuguchi et al, 2016; Dore et al, 2015; Marshall et al, 2016; Stubbs et al, 2015; Leveille et al, 2009; Patel et al, 2014). One study (Leveille et al, 2002) explored the relationship between musculoskeletal pain and falls by categorising pain into widespread pain, moderate or severe pain in at least one region of the body (but not fulfilling widespread pain) and 'other pain' that did not fit into the aforementioned categories (Leveille et al, 2002). Two studies (Ho et al, 1996; Bebikele et al, 2010) set out to explore correlates of falls and included the covariate of pain. Two studies explored specific body sites and their relationship with falls (Harada et al, 2015: knee pain and low back pain; Holt et al, 2011: neck pain and back pain). Six studies explored risk factors for falls in populations with painful conditions and included a measure of pain sites as a covariate. Oswald et al (2006), Stanmore et al (2013), Brenton-Rule et al (2016) and Hayashibara et al (2010) investigated populations with rheumatoid arthritis, Furuya et al (2009) explored falls risk in those with polyarthritis and Jones et al (2011) and Goes et al (2012) investigated those with fibromyalgia.

Figure 5.2 Summary of the systematic review search process for multisite pain and falls

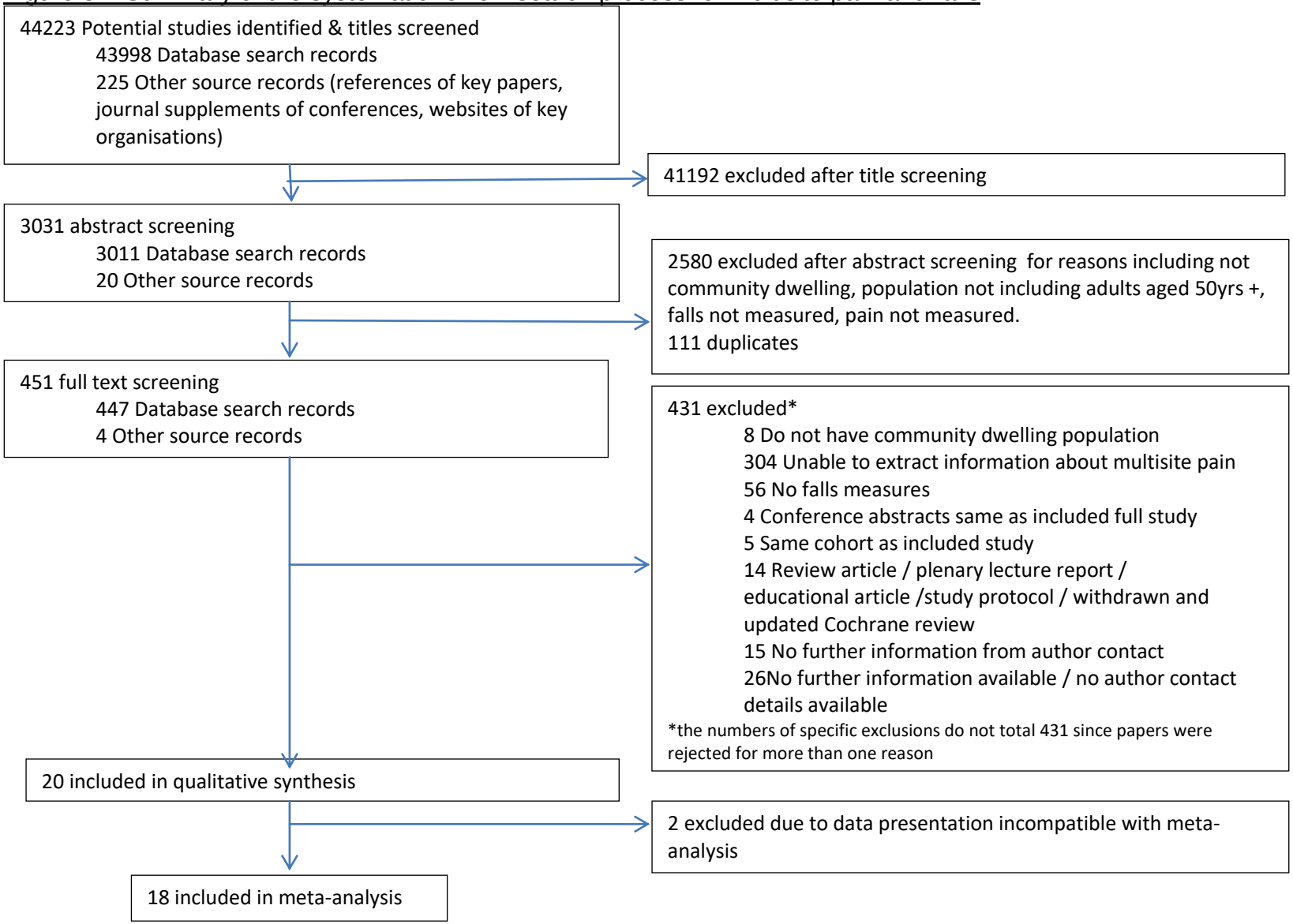


Table 5.1 Articles included in the systematic review: key study characteristics

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Ho et al, 1996	Hong Kong; nationwide	Cross-sectional	n = 1947 Men and women Aged 70 years and older	Musculoskeletal pain in different sites experienced in the previous month Single site and multisite pain measurements	Retrospective: falls in the previous 12 months	The Croucher Foundation, United Kingdom
Leveille et al, 2002	United States; community	Prospective cohort	n = 940 Older women with disability Widespread pain group mean age 76.5 years (SD 7.3) Comparator group mean age 80.2 years (SD 8.1)	Pain in the hand, wrist, back, chest (excluding angina), hip, knee or foot on most days for at least a month in the previous year Single site pain (moderate or severe lower extremity pain (hip, knee or foot)) Multisite pain (widespread musculoskeletal pain (pain in upper extremities (hand or wrist) and lower extremities (hip, knee or foot) and axial skeleton (back or chest) with at least moderate pain (score >4 on numerical rating scale) in one site) No pain or only mild pain (score <4 on numerical rating scale)	Retrospective: falls in the previous 6 months prior to follow up; six-monthly follow-up over 3 years	National Institute on Ageing

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Oswald et al, 2006	United Kingdom; outpatient rheumatology clinic	Cross-sectional	n = 316 Women with established inflammatory polyarthritis satisfying American Rheumatism Association criteria Mean age 59 years (SD 13.2)	Presence and total number of tender joints	Retrospective: falls in the previous 12 months	Not explicitly stated
Furuya et al, 2009	Japan; outpatient rheumatology clinic	Cross-sectional	n = 4996 Men and women with rheumatoid arthritis satisfying American College of Rheumatology definition Median age 60 years (range 49-74.8 years)	Presence and total number of tender joints	Retrospective: falls in the previous 6 months	'36 pharmaceutical companies' and a grant from the Japanese Osteoporosis Foundation

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Leveille et al, 2009	United States; community	Prospective cohort	n = 749 Men and women Mean age 78 years (SD 5years)	Pain for at least 3 months in the previous year in hands, wrists, shoulders, back, hips, knees, feet, chest (excluding angina). Multisite pain (pain in two or more locations); single site pain (pain in a single location); no pain	Prospective: monthly falls postcards completed daily	National Institute on Aging Coding of medication data supported by grant from Pfizer (non of which supported salary, stipends or other funding except salaries of researchers)
Bebikele & Gureje, 2010	Nigeria; community	Cross-sectional	n = 2096 Men and women aged 65 years and older Mean age of fallers 75.2 years; mean age of non-fallers 75.1 years	Pain in back, neck, chest, joints, headache and 'persistent pain in any other part of the body' experienced in previous 12 months. No pain, single site pain (pain in a single location) and multisite pain (pain in two or more locations)	Retrospective: falls in the previous 12 months	Wellcome Trust
Hayashi-bara et al, 2010	Japan; outpatient rheumatology clinic	Prospective cohort	n = 84 Women with 'definitive diagnosis' of rheumatoid arthritis Mean age 65.3 (range 50-82 years)	Tender joint count	Prospective: monthly falls calendars completed daily	Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Holt et al, 2011	New Zealand and Australia; community chiropractor clinics	Cross-sectional	n = 101 Men and women Mean age 72 years (standard deviation 5.9, range 65-92 years)	Presence or absence of back and/or neck pain Multisite pain (pain in the neck and back); single site pain (pain in back or neck); no pain	Retrospective: falls in the previous 12 months	Grant from the Australian Spinal Research Foundation
Jones et al, 2011	United States; Outpatient fibromyalgia clinic & local university	Case-control	n = 52 (27 fibromyalgia, 25 health controls) Men and women Cases: fibromyalgia diagnosed according to American College Rheumatologists' definition Healthy controls Mean age 48.6 years (standard deviation 9.7, range 30-59 years)	Number of painful body regions recorded on body diagram Mean number of painful body regions in fibromyalgia and control group reported	Retrospective: falls in the previous 6 months	National Institutes of Health, Fibromyalgia Information Foundation

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Goes et al, 2012	Brazil; inpatient rheumatology ward and local community	Case-control	n = 32 (16 fibromyalgia, 16 health controls matched for BMI, age and physical activity) Women Cases: fibromyalgia diagnosed according to American College of Rheumatology definition Healthy controls Age range 29 – 50 years; mean age fibromyalgia group 41.5years (standard deviation 5.92); mean age control group 40.4years (standard deviation 6.45)	Presence of pain on the day of study: presence of tender points in lower limbs and general pain	Falls in the previous 6 months	Grant from the Coordination for the Improvement of Higher Education Personnel, Brazil
Dore et al, 2015	United States, community	Prospective cohort study	n = 1619 men and women, African-American or Caucasian with or without OA mean age 62 years (range 45-89)	Symptomatic OA for left or right hip or knee - presence of pain, aching or stiffness on most days and associated with radiographic changes. Categorised into symptomatic OA / mild symptoms / moderate or severe symptoms and Kellgren/Lawrence grade >=2 at hip or knee.	Retrospective recall of falls of any type in the previous 12 months and number of falls.	National Center for Advancing Translational Sciences/NIH, CDC/Association of Schools of Public Health and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Stan-more et al, 2013	United Kingdom, Rheumatology out patient clinics	Prospective cohort study	n=535 men and women all with rheumatoid arthritis defined by American College of Rheumatology mean age 62 years (48-75 years)	Number of swollen or tender joints	Prospective: monthly falls calendars completed daily over 12 months	Arthritis Research UK, Wellcome Trust Clinical Research Facility, Manchester.
Patel et al, 2014	United States, community or residential setting	Cross sectional survey	n=7601 men and women older people receiving Medicare aged 65yrs and over	Bothered by pain in the last month and indication of pain site on a card	Retrospective: falls in the previous 12 months and how many	National Insitute on Aging through cooperative agreement with the John Hopkins Bloomberg School of Public Health
Harada et al, 2015	Japan, community setting	Cross sectional survey	n=1351 men and women able to partake in physical activity aged 65-74 years	Experience of knee pain or low back pain in the past month	Retrospective: falls in the previous 12 months	Grant-in-Aid for Research Fellows of the Japan Society for the Promotion of Science; Waseda University Grant for Special Research Projects; Global COE Program "Sports Sciences for the Promotion of Active Life" from the Japan Ministry of Education, Culture, Sports, Science and Technology.

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Asai et al, 2015	Japan, local community association centre	Cross sectional survey	N=112 Men and women with normal motor function Mean age 73.5 years (68.9 – 78.1 years)	Presence of pain at back, hip, knee, foot or toe, lasting 1 month or more in the previous year and also present in the previous month. Number of pain sites counted and grouped into no pain, single-site pain and 2 or more pain sites	Retrospective: falls in the preceding 12 months	This study was supported by a Grant-in-Aid for Young Scientists (B) (22700685) from KAKENHI in Japan.
Kitayug-uchi et al, 2015	Japan, general community attending falls prevention clinic	Cross sectional survey	N = 491 Men and women aged 60 years and older Mean age 72.2 (66.2-78 years)	How much low back pain and knee pain experienced in the last week: none, mild, severe, very severe. Mild to very severe classed as 'pain' group.	Falls in the last 12 months	Not explicitly stated.
Stubbs et al, 2015	UK, community setting	Cross sectional survey	N = 295 Men and women Mean age 77.5 years (69.4 – 85.6 years)	Report of musculoskeletal pain present over the past month and for at least 3 months of the previous year. Classified into no chronic musculoskeletal pain (CMP), single site CMP and multisite CMP	Retrospective recall of falls over the preceding 12 months	Vice Chancellor's scholarship at the University of Greenwich

Author	Study setting	Study type	Study population	Pain measurement and classification	Falls measure	Funding source
Marshall et al, 2016	USA, community setting	Prospective cohort study	N= 6,841 Women aged 65 years and older Mean age 73.1 years (standard deviation 5.0, 4.8)for the no pain group and mild pain group. 73.3 years (4.9) for the moderate pain group and 73.7 years (standard deviation 5.1) for the severe pain group	'Any back pain in the last 12 months?'. Those reporting 'yes' marked on a drawing where their back pain usually occurred (upper, middle, lower). This was classified into lower back only, upper back only, mid back only, and number of pain sites as 1, 2 and 3. Presence or absence of hip pain	Retrospective recall of fall and number of fall every 4 months following baseline	The Study of Osteoporotic Fractures is supported by the National Institute on Aging through grant numbers R01 AG005407, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, and R01 AG027576.
Kitayug-uchi et al, 2016	Japan, community based	Prospective cohort study	N = 1890 Men and women Mean age 68.3 years (SD 5.9 years)	Low back pain (LBP) and knee pain (KP) presence. Pain classified into current pain lasting longer than 3 months, current pain lasting less than 3 months, no pain. Multisite pain defined as no chronic LBP or KP, either chronic LBP or KP, both LBP and KP.	Retrospective recall of falls over the past 12 months	This study was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare of Japan (H20-Junkankitou-Ippan-001).
Brenton-Rule et al, 2016	New Zealand rheumatology outpatient department	Cross sectional study	N= 201 Men and women Mean age 64.7 years (SD 11) All participants have rheumatoid arthritis	Tender joint count: total and lower limb.	Retrospective: falls in the past 12 months and number of falls	Arthritis New Zealand and the Health Research Council of New Zealand
SD = standard deviation; OA = osteoarthritis						

5.8.3 Study design

Three different study designs were employed. Eleven studies used a cross-sectional design (Ho et al, 1996; Oswald et al, 2006; Furuya et al, 2009; Bebikele et al, 2010; Holt et al, 2011; Patel et al, 2014; Harada et al, 2015; Asai et al, 2015; Kitayuguchi et al, 2015; Stubbs et al, 2015; Brenton-Rule et al, 2016), seven used a prospective cohort approach (Leveille et al, 2002; Leveille et al, 2009; Hayashibara et al, 2010; Dore et al, 2015; Stanmore et al, 2013; Marshall et al, 2016; Kitayuguchi et al, 2016) and two utilised a case-control study design (Jones et al, 2011; Goes et al, 2012).

5.8.4 Study population

15 studies investigated falls risk in men and women (Leveille et al, 2009; Ho et al, 1996; Furuya et al, 2009; Bebikele et al, 2010; Holt et al, 2011; Jones et al, 2011; Dore et al, 2015; Stanmore et al, 2013; Asai et al, 2015; Kitayuguchi et al, 2015; Kityuguchi et al, 2016; Patel et al, 2014; Stubbs et al, 2015; Harada et al, 2010; Brenton-Rule et al, 2016) and five studies included only women (Leveille et al, 2002; Oswald et al, 2006; Hayashibara et al, 2010; Goes et al, 2012; Marshall et al, 2016).

Twelve study populations are aged 65 years and older (Kitayuguchi et al, 2015; Kitayuguchi et al, 2016; Marshall et al, 2016; Stubbs et al, 2015; Harada et al, 2010; Leveille et al, 2002; Leveille et al, 2009; Bebikele et al, 2010; Holt et al, 2011; Patel et al, 2014; Ho et al, 1996; Asai et al, 2015). The remaining study populations are made predominantly of adults aged 50 years and older, although seven studies included a small number of younger participants (Stanmore et al, 2013; Oswald et al, 2006; Furuya et al, 2009; Jones et al, 2011; Hayashibara et al, 2010; Goes et al, 2012; Dore et al, 2015).

The total number of study participants is 32,203. The largest study included 7601 participants in the analysis (Patel et al, 2014) and the smallest study included 32 participants (Goes et al, 2012).

5.8.5 Pain measurement

Pain was defined in different ways using varying time frames and body sites.

Regarding time frame, pain presence ranged from simply the 'presence of pain' (Holt et al, 2011), to 'pain experienced in the last week' (Kitayuguchi et al, 2015), 'pain in the last 12 months' (Marshall et al, 2016) and 'pain experienced for at least three months in the previous year' (Leveille et al, 2009). Three studies classified the pain group as those reporting pain in the previous month (Ho et al, 1996; Patel et al, 2014; Harada et al, 2015). Some definitions incorporated the requirement of current pain alongside a history of pain in the preceding year (Asai et al, 2015; Stubbs et al, 2015; Kitayuguchi et al, 2016). Some studies used varying definitions to elicit chronic pain pictures rather than acute episodes, for example 'persistent pain' (Bebikele et al, 2010), 'pain on most days for at least a month (Leveille et al, 2002), pain lasting for one month or more (Asai et al, 2015) and pain lasting for at least three months (Stubbs et al, 2015; Leveille et al, 2009). Studies investigating specific populations used disease-specific measures, for example the presence and number of tender joints for studies investigating inflammatory arthritides (Oswald et al, 2006; Furuya et al, 2009; Hayashibara et al, 2010; Stanmore et al, 2013; Brenton-Rule et al, 2016) and a diagnosis of fibromyalgia (Goes et al, 2012, Jones et al, 2011). One study used pain in

associated with radiographic changes to define the pain population (Dore et al, 2015).

Categorisation of multisite pain varied between studies. Some studies included severity of pain as part of their classification, for example Leveille et al (2002) grouped pain into widespread pain which included at least moderate pain in one region, lower extremity pain and a pain reference group of no pain or mild pain (scoring less than 4 on a numerical pain scale).

Some studies included contribution of pain in many different parts of the body to total number of pain sites and multisite pain status; some studies investigated specific body sites. Most studies surveyed their participants using specific questions about body parts. Two studies (Goes et al, 2012; Marshall et al, 2016) included a body manikin for participants to highlight pain sites.

All included studies used a group that reported no pain as the comparator group.

5.8.6 Falls measurement

Nine studies provided no formal definition of falls (Leveille et al, 2002; Oswald et al, 2006; Furuya et al, 2009; Bebikele et al, 2010; Holt et al, 2011; Dore et al, 2015; Harada et al, 2015; Asai et al, 2015; Marshall et al, 2016) and five studies used the gold standard PRoFaNE definition (Hauer et al, 2006) (Leveille et al, 2009; Stanmore et al, 2013; Kitayuguchi et al, 2015; Stubbs et al, 2015; Kitayuguchi et al, 2016; Brenton-Rule et al, 2016). The remaining five studies provided definitions that were adapted from the gold standard definition (Hayashibara et al, 2010; Jones et al, 2011; Goes et al, 2012, Ho et al, 1996; Patel et al, 2014).

The majority of studies collected retrospective information on falls in the preceding 12 months (Ho et al, 1996; Oswald et al, 2006; Bebikele et al, 2010; Holt et al, 2011; Dore et al, 2015; Patel et al, 2014; Harada et al, 2010; Asai et al, 2015; Kitayuguchi et al, 2015; Stubbs et al, 2015; Kitayuguchi et al, 2016; Brenton-Rule et al, 2016). Four studies requested retrospective information on falls in the preceding 6 months (Leveille et al, 2002; Furuya et al, 2009; Jones et al, 2011; Goes et al, 2012) and Marshall et al (2016) requested falls information every four months following study baseline.

Three studies used the gold standard method of prospective falls data collection through the use of a falls calendar that is completed daily (Leveille et al, 2009; Hayashibara et al, 2010; Stanmore et al, 2013).

5.8.7 Quality Appraisal

Table 5.2 provides a summary of the QUIPS assessment; more detailed analyses are found in Appendix 3.

Study participation descriptions were generally of low quality, with 80% of studies providing inadequate information about the source population or providing details of study sampling frame and recruitment.

Study attrition scored as high risk of bias across all studies; response rate was documented in seven studies and other measures including information on participants who dropped out the study were poorly recorded; no studies provided enough information to be confident of a low risk of bias due to study attrition.

Prognostic factor measurement was of higher quality, with 50% of individual studies defining pain and its measurement detail and 45% providing partial

explanations. Eight studies provided information on the proportion of pain data for analysis and 12 studies did not. Overall, the domain of pain measurement conferred the lowest risk of bias, with half of studies achieving a 'yes' score (meaning that the prognostic factor was adequately measured to sufficiently limit potential bias).

Falls measurement was a potentially significant source of bias amongst studies, with only 15% of studies provided a description of falls adequate to limit potential bias. The primary problem was the underreporting of falls definitions (55% of studies) and the reliance on recall for falls (85%).

The domain addressing study confounders scored low across most categories and in overall scores, with only two studies providing enough information to sufficiently limit potential bias. The main problems were failure to measure important confounders, failure to describe the measurement or use reliable measures and, most crucially failure to discuss missing confounder data (18 from 20 studies). The consideration of study confounders is therefore a potentially significant source of bias.

Statistical reporting was more reliably recorded, with 50% of studies reporting information sufficient to limit the potential bias.

Nine studies were deemed to be at high risk of bias, seven studies were judged to be of medium risk and four studies had a low risk of bias. The domain conferring the highest risk of bias was study attrition, with no studies achieving the level required to limit the potential bias. Falls outcome measurements, confounder measurements and study participation are also areas in which the potential for

bias is not limited in 80% or more studies. Statistical reporting and measurement of pain found 50% of studies to be at risk for potential bias within these domains.

Overall, the quality appraisal has found that each domain has the potential to introduce bias and the majority of studies are judged to be of either high or medium risk of bias; results of the systematic review and meta-analysis must therefore be interpreted with this in mind.

Table 5.2 Summary of the quality appraisal assessment for studies included in the multisite pain and falls systematic review

QUIPS assessment domain							
Author	**Study participation**	**Study attrition**	**Measure of Pain**	**Measure of Falls**	**Study confounding**	**Statistical analysis & reporting**	**Summary of bias**
Leveille et al, 2002	Yes	Unclear	Yes	Partial	Partial	Yes	Medium
Oswald et al, 2006	Unclear	Partial	Yes	Partial	Partial	Yes	High
Furuya et al, 2009	Unclear	Unclear	Partial	Partial	Partial	Partial	High
Leveille et al, 2009	Yes	Unclear	Yes	Yes	Yes	Yes	Low
Bekibele & Gureje 2010	Yes	Unclear	Partial	Partial	Yes	Partial	Medium
Hayashibara et al, 2010	Unsure	Unsure	Yes	Yes	Partial	Yes	Low
Holt et al, 2011	Unclear	Unclear	Partial	Partial	No	Partial	High
Jones et al, 2011	Partial	Unclear	Yes	Partial	No	Partial	High
Goes et al, 2012	unclear	Unclear	Partial	Partial	Partial	yes	High
Ho et al, 1996	Unclear	Unclear	no	Partial	Partial	Partial	High
Dore et al, 2015	Partial	Unclear	Partial	Partial	Partial	yes	Medium
Stanmore et al, 2013	Partial	No	Yes	Yes	Partial	yes	Low
Patel et al, 2014	yes	Partial	Partial	Partial	Partial	yes	Low
Harada et al, 2015	unclear	unclear	Partial	Partial	No	yes	High
Asai et al, 2015	unclear	unclear	Partial	Partial	Partial	yes	High
Kitayugachi et al, 2015	unclear	unclear	yes	Partial	Partial	Partial	High
Marshall et al, 2016	unclear	Unclear	yes	Partial	Partial	Partial	Medium
Stubbs et al, 2015	Partial	unclear	Partial	Partial	Partial	Partial	Medium
Kitayuguchi et al, 2016	Unclear	unclear	yes	Partial	Partial	Partial	Medium
Brenton-Rule et al, 2016	Unclear	Unclear	Yes	Partial	Partial	Partial	Medium

5.8.8 Systematic review results

Fourteen studies demonstrated a statistically significant association between the presence of multisite pain and falls when adjusting for confounding factors; six studies found no statistically significant relationship between multisite pain and falls after adjusting for confounders. The study with the lowest overall risk of bias rating was Leveille et al (2009), who found that pain in two or more locations had a relative risk of 1.53 (1.17-1.99) for future falls risk when adjusted for socioeconomic variables, chronic conditions, physical and cognitive status, physical performance and psychotherapeutic medications, analgesic use and hand and knee arthritis.

Studies designed to measure a potential dose-response relationship found that the more pain sites experienced, the higher the risk of falls (Dore et al, 2015; Leveille et al, 2002; Patel et al, 2014; Marshall et al, 2016); for example Patel et al (2014) found a dose-response relationship between number of pain sites and cross-sectional self-reported falls, with the prevalence ratio rising from 1.53 (1.31-1.79) for those reporting two pain sites, to 1.75 (1.51-2.04) for those reporting four pain sites.

This systematic review suggests that multisite pain does increase the risk of falls in both cross-sectional and prospective analyses. There is wide variation however between study design, populations, pain and falls measurements and 80% of studies were considered to be at medium or high risk of bias. A meta-analysis was performed to assimilate individual risks and produce a summary effect estimate to better understand the association between pain and falls.

5.8.9 Meta-analysis results

5.8.9.1 Multisite pain and falls: unadjusted summary statistic

The D&L pooled estimate summary for the unadjusted association between multisite pain and falls is 1.83 (1.54-2.19), meaning that the presence of multisite pain is associated with almost double the risk of falls compared with a no-pain group. Figure 5.3 provides a Forest plot of individual study effect estimates and the pooled effect estimate along with corresponding weightings.

Heterogeneity is likely to have significantly affected the pooled estimate with an I^2 of 69.2% and a Cochran Q probability of <0.01.

Those studies presenting only mean tender joint counts (Hayashibara et al, 2010; Brenton-Rule et al, 2016) or where odds ratios are not able to be calculated (Patel et al, 2014) are not included in the pooled estimate. Ho et al (1996) had bilateral wrist pain included in the unadjusted analysis and chronicity multisite measure was used from Kitayuguchi et al (2016).

Publication bias is assessed by the funnel plot in figure 5.4. The funnel plot appears asymmetrical with four points lying outside the 95% confidence interval, three of which lie on the side where the OR>1. This indicates possible publication bias supported by Egger's test statistic where p=<0.01. Begg's test however gives a p=0.22, demonstrating the potential instability of the test when a small number of studies are included.

Figure 5.3 Meta-analysis of the unadjusted odds for multisite pain and falls in cross-sectional, cohort and case-controlled studies

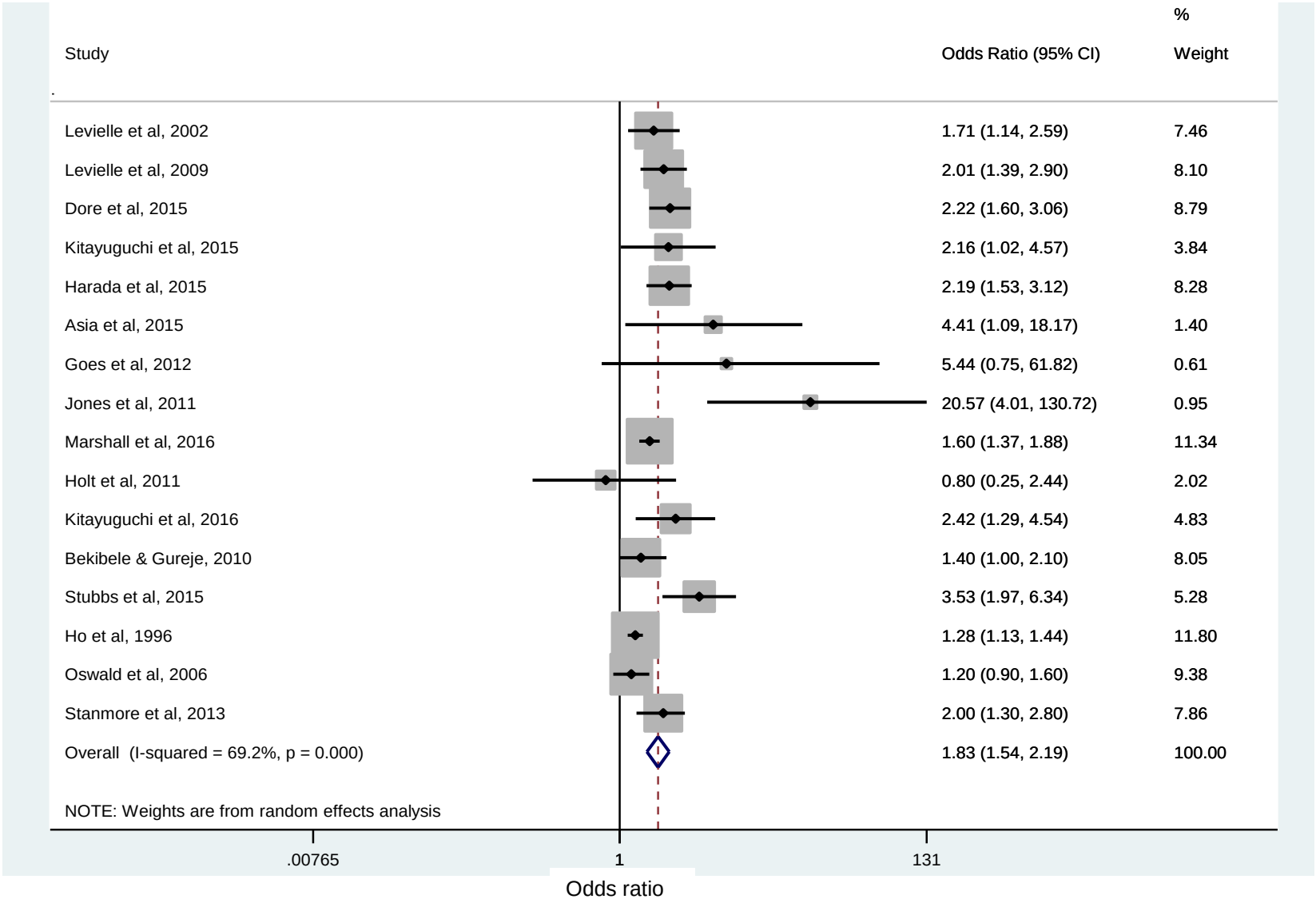
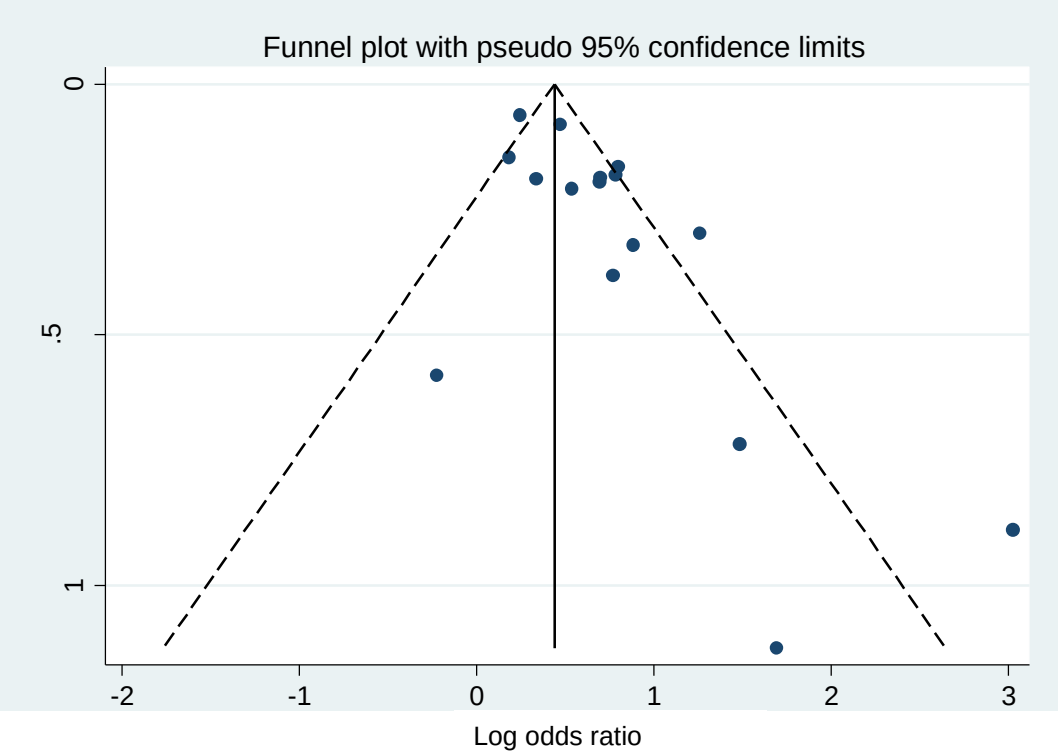


Figure 5.4 Funnel plot of publications examining the unadjusted relationship between multisite pain and falls for cross-sectional, cohort and case-controlled studies



5.8.9.2 Multisite pain and falls: adjusted summary statistic

Studies were included in this summary statistic if risk estimates were provided that had been adjusted for confounding factors and potential influencing covariates. Table 5.3 lists the covariates that were taken account of during analysis in one or more studies.

The D&L pooled estimate summary for the adjusted association between multisite pain and falls is 1.56 (1.40-1.75), meaning that the presence of multisite pain is statistically significantly associated with the risk of falls when compared with a no-pain group. Figure 5.5 provides a Forest plot of individual study effect estimates and the pooled effect estimate along with corresponding weightings.

Heterogeneity is unlikely to have significantly affected the pooled estimate with an I^2 of 0.0% and a Cochran Q probability of 0.64.

The funnel plot in figure 5.6 shows all points remain within the 95% confidence intervals and publication bias is therefore less likely to be significantly impacting results, although there does appear to be asymmetry with skewing towards an effect size of >1; Begg's test p=0.09 and Egger's test p=<0.01 indicated that there is a risk of publication bias that must be taken account of during results interpretation.

Table 5.3 Putative confounders and influencing covariates that were adjusted for in one or more study

Group	Variables
Demographics	Demographics: Age Sex Ethnicity Education
Physical health	BMI, Mediation conditions (hip fracture, angina pectoris, diabetes mellitus, peripheral arterial disease, stroke, Parkinson's disease, depression, lung problems, neurological problems, TKR, THR, Smoking, Dizzy or unsteadiness, Fatigue score DAS28 score)
Mental health	self-reported psychological distress, Cognitive functioning
Medication use	psychoactive medications, daily use of analgesic medications, total number , narcotic use , taking 4+ medications, steroids , NSAID use, osteoporosis drug use, vitamin D3 use
Physical functioning	Walking disability , lower limb functional decline
Fall-related history	Previous falls, fear of fall, History multiple falls History of injuries from previous fall
Physical tests	gait speed, balance test score, exercise time , timed up and go test , Four-test balance scale , chair stand test
Blood tests	ESR CRP
Self-rated scoring	Self-rated health & health related quality of life
THR = total hip replacement; TKR = total knee replacement; DAS28 = disease activity score 28; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein	

Figure 5.5 Meta-analysis for the adjusted odds for multisite pain and falls in cross-sectional, cohort and case-controlled studies

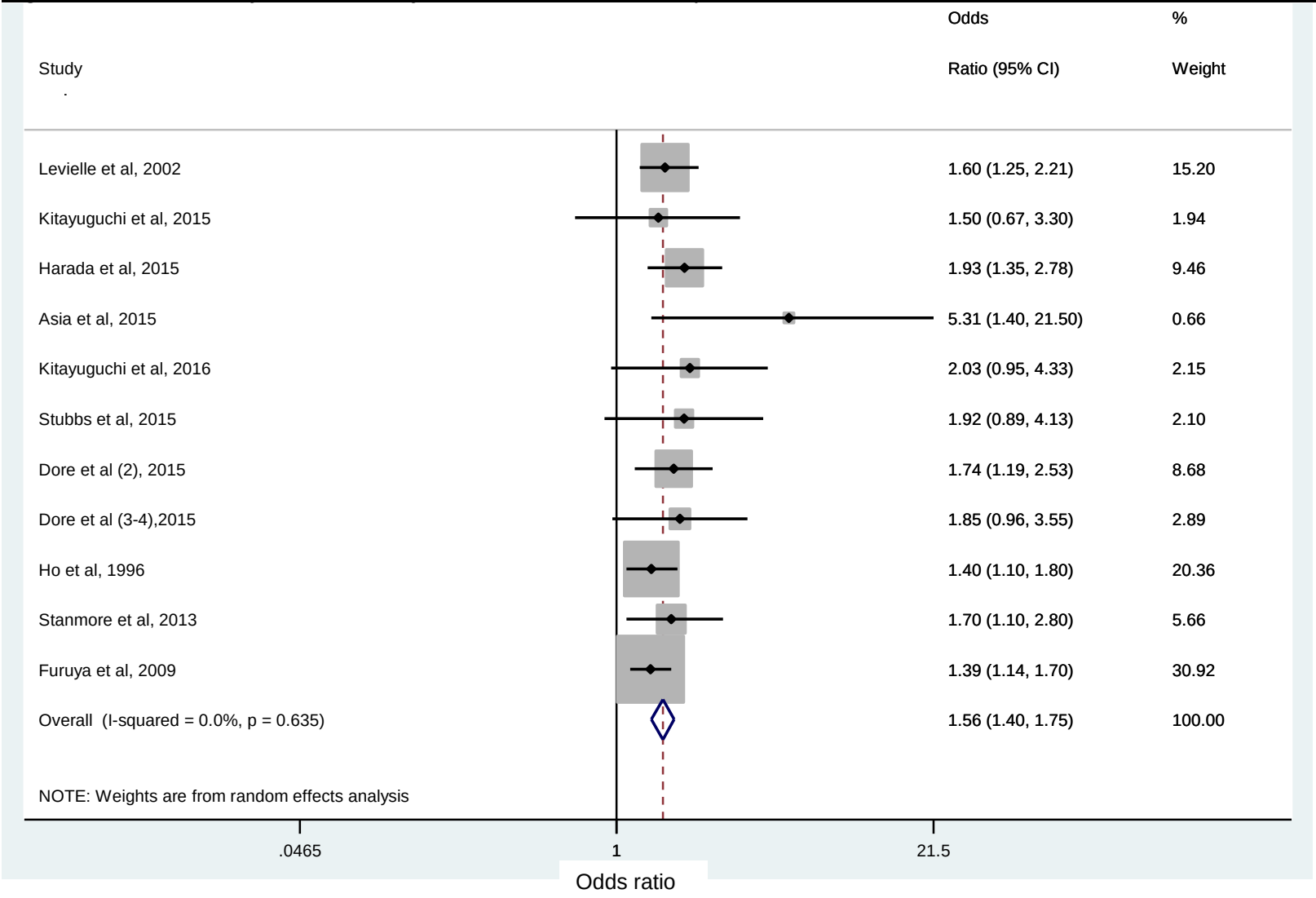
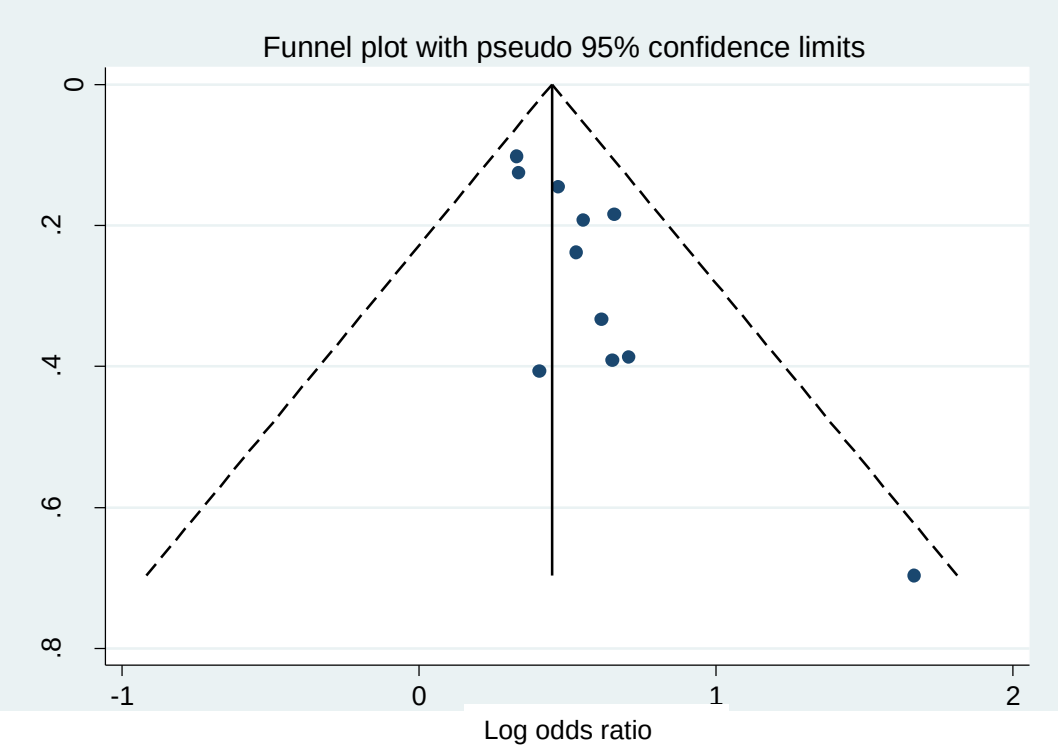


Figure 5.6 Funnel plot of publications examining the unadjusted relationship between multisite pain and falls for cross-sectional, cohort and case-controlled studies



5.8.9.3 Multisite pain and falls: summary statistic from prospective cohort studies

Prospective cohort studies were included in this analysis. Five studies were eligible for inclusion, one study did not have an odds ratio or raw data to enable odds ratio calculation (Hayashibara et al, 2010) and two studies had unadjusted and adjusted risk estimates available (Leveille et al, 2002 and Stanmore et al, 2013). The unadjusted analysis is presented by the Forest plot in figure 5.7. The D&L pooled estimate summary for the association between multisite pain and future falls is an odds ratio of 1.70 (1.49-1.94), meaning that the presence of

multisite pain is associated with an increased odds of future falls compared to those with no pain. Heterogeneity is unlikely to have significantly affected the pooled estimate with an I^2 of 0.0% and a Cochran Q probability of 0.57.

The funnel plot for this analysis shows all points remain within the 95% confidence interval and there is no asymmetry. Begg's test has a p=1.00, demonstrating that this test is not useful in small analyses with less than 10 studies included (Sterne et al, 2011). Egger's test has a p=0.15 which suggests that publication bias does not pose a significant problem within this analysis.

The adjusted analysis, presented by the Forest plot in figure 5.8, provides a summary effect estimate of OR 1.63 (1.28-2.07), with an I^2 of 0.0% and a Cochran Q probability of 0.83. Since the analysis includes only two studies, testing for publication bias is not undertaken.

Figure 5.7 Meta-analysis of the unadjusted odds of multisite pain and falls in prospective cohort studies

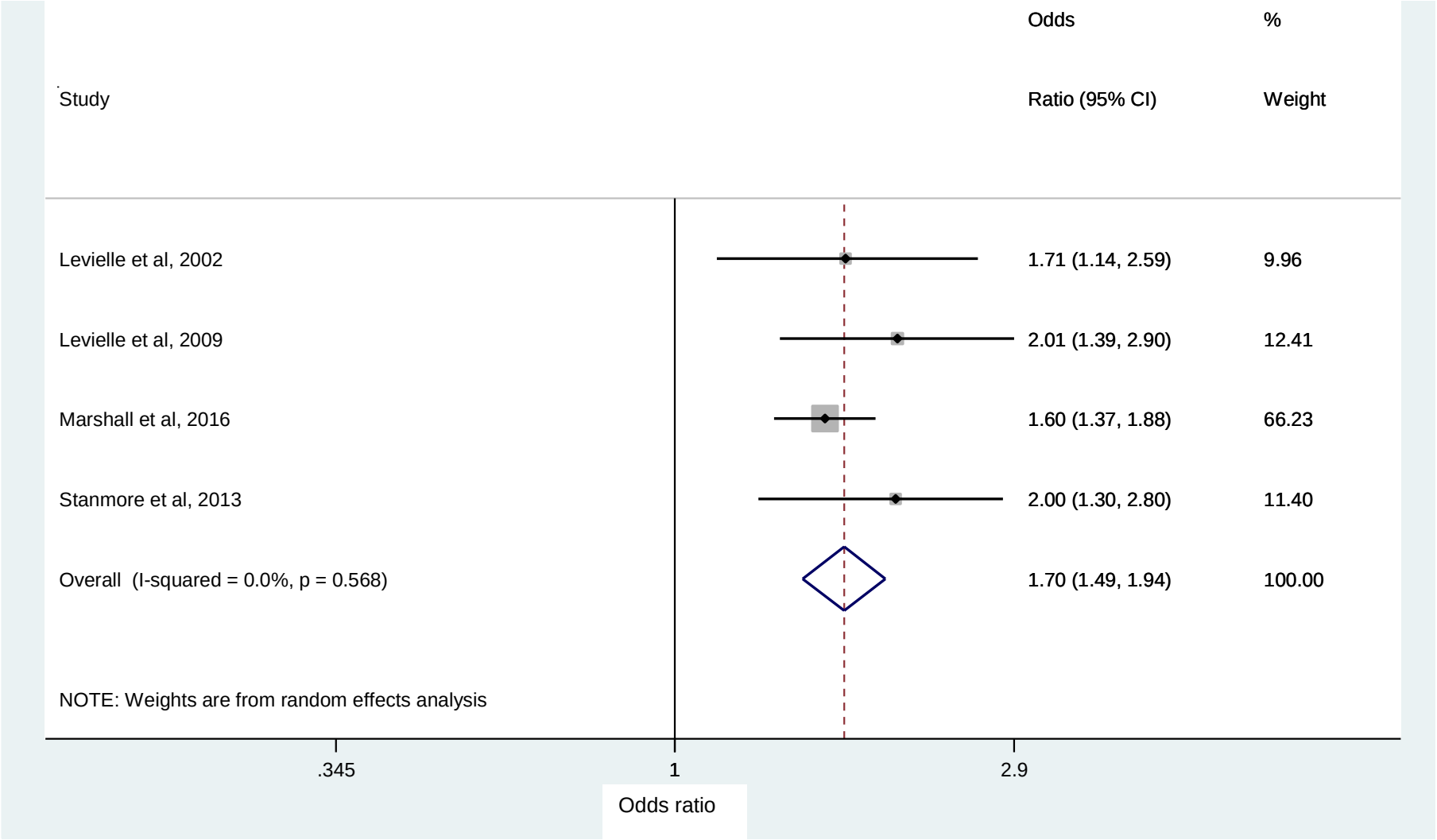
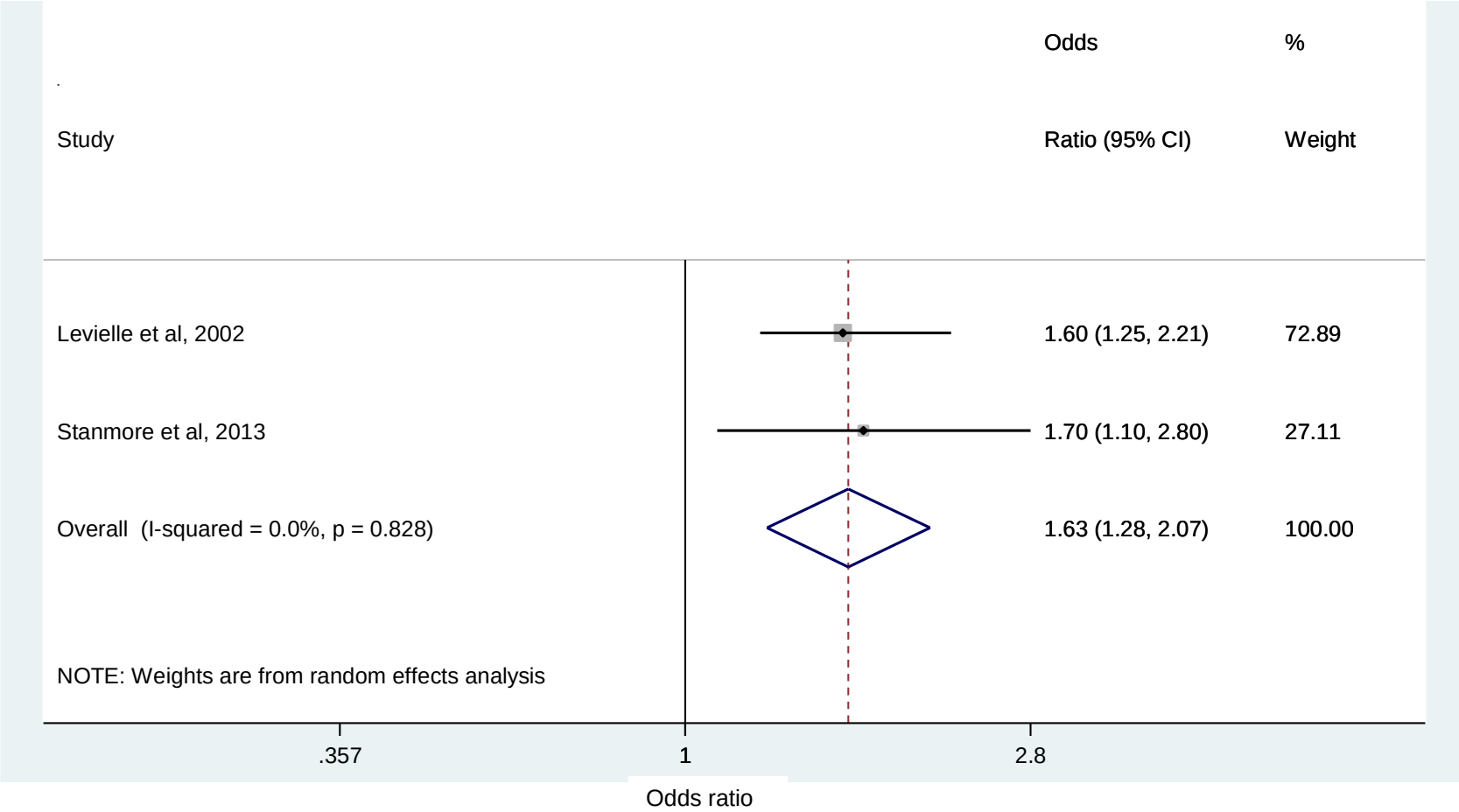


Figure 5.8 Meta-analysis of the adjusted odds of multisite pain and falls for prospective cohort studies



5.9 Discussion

5.9.1 Summary of findings

Older people with multisite pain have statistically significant increased odds of falling when compared to their pain-free counterparts. The unadjusted analysis of all study designs found that those with multisite pain had an odds ratio of 1.83 (1.54-2.19), this reduced to 70% increased odds of falling in the unadjusted analysis for prospective cohort studies only and further reduced, although remained statistically significant, to 50% increased odds of falling compared to those with no pain.

5.9.2 Strengths

This systematic review and meta-analysis is comprehensive, drawing on evidence from many different sources and not imposing language limitations. The broad search strategy ensured maximum capture of relevant research and the rigorous approach enabled the huge volume of titles to be managed efficiently.

The inter-rater concordance of 100% at each stage of the review demonstrates a high level of internal validity. The large volume of references resulted in referencing software instability and an inability to remove duplicates until a late stage in the review process; this meant that references were likely to be reviewed twice, thus increasing the likelihood that important references were not missed.

The systematic review and meta-analysis includes a variety of different pain phenotypes (for example, hip, knee, lower limb, back, neck, widespread pain) and a variety of diagnoses were used to derive study samples (for example, osteoarthritis and rheumatoid arthritis) thus representing a wide spectrum of pain presentations. Furthermore, the review included swollen or tender joint count as a

measure of multisite pain to ensure that specific types of pain (e.g. inflammatory) were not excluded. The purpose of this thesis is to measure the impact of the global burden of pain on falls risk regardless of pathology, thus different pathological conditions are included. Excluding studies only including those with rheumatoid arthritis on the basis of a potentially different or exaggerated pathophysiological process contributing to falls risk (for example, inflammatory responses and specific joint erosions contributing to falls risk which may not be present in those without rheumatoid arthritis) would mean excluding any specific pathological conditions and thus render the exercise clinically illiterate. Nevertheless, these different pathological processes must be considered in interpretation of findings. In this review, the risk of falls associated with tender or swollen joint count did not cluster around one value and was spread throughout the other studies' risk estimates; thus including this measure reflects clinical practice and does not appear to bias results.

Although there are significant differences between studies in terms of study design, pain measures, falls outcomes and consideration of putative confounders and a high I^2 score for the unadjusted analysis, the adjusted analysis has an $I^2 = 0$ and is therefore less likely to be affected by heterogeneity, thus meaning that results can be more confidently accepted.

5.9.3 Limitations

The large number of references to screen conferred a risk that important references were overlooked as they were nested within thousands of irrelevant titles. The risk was minimised by self-awareness and careful consideration of

each title, the likelihood of references being reviewed twice due to duplication and the high inter-rater reliability.

The review includes cross-sectional studies in which causality cannot be measured, since it is not possible to know that the pain reported simultaneously with falls occurred before or after the fall. Stubbs et al (2015) removed this risk in his cross-sectional study by specifically asking those who had fallen and reported pain if the pain had occurred as a consequence of the fall and then excluding those who replied that it had. Cross-sectional studies were included to increase the number of studies and therefore power of the analysis since there were only five prospective cohort studies included in the final 20 articles. The inclusion of cross-sectional studies means a more precise overall summary estimate of the (strength of) association between multisite pain and falls can be measured; the analysis confined to prospective studies is indicative that multisite pain is a risk factor for future falls.

The risk of bias of included studies was significant, particularly for study participation and outcome measurement. Some studies did not report response rates and attrition rates and reasons were unclear. If those not partaking in the study, or dropping out during follow up are doing so because of advancing age, poorer health and increased frailty compared to participants, this may underestimate the risk of falls since those more likely to fall (due to advancing age, poor health and increased frailty) are not included in the study. 85% of studies relied on recall of previous falls; the problems associated with this recall bias are well documented, for example Hannan et al (2010) found that people over aged 70 were able to recall 70% of all falls that had occurred in the previous three month period and, of those who fell, 25% were misclassified as non-fallers (Hannan et al,

2010). Therefore, use of retrospective falls recall may underestimate the true effect estimate of pain on falls.

5.9.4 Identifying the knowledge gap

The most significant gap in the literature is the lack of large, long duration prospective cohort studies examining the relationship between pain status and future falls risk. Five studies in the review were prospectively designed to capture future falls risk, four of which were included in the meta-analysis which exclusively included prospective studies. The prospective cohort studies had a range of sample sizes from n=84 to n=6,841; only one study (Marshall et al, 2016) contained more than 1,000 participants. The longest studies followed participants for three years (Leveille et al, 2009; Leveille et al, 2002).

A further significant gap in the literature examining the association between multisite pain and falls is the lack of variation in the falls outcome. All of the studies used self-reported falls as the outcome measure, with little or no indication of fall severity, associated health-care use or injury. It is therefore not possible to ascertain the consequences of the reported falls.

Finally, the risk of bias attributed to the handling of putative confounders was high, with 18 from 20 studies judged to provide insufficient evidence such that risk of bias was not sufficiently limited; thus there appears to be a lack of studies taking account of confounding.

5.9.5 Addressing the knowledge gap

This thesis will seek to address these knowledge gaps by using a prospective design with a large sample size with a longer follow period than is currently found in the evidence base. Different 'types' of falls will be explored to examine differences in their relationship with multisite pain and a variety of putative confounders will be considered to reduce the risk of bias due to confounding.

5.9.6 Summary

This chapter has described the process and results of a systematic review and meta-analysis of multisite pain and falls in older people. Multisite pain is associated with an increased odds of falling in unadjusted and adjusted analyses and the pooled summary estimate for prospective cohort studies found that the presence of multisite pain predicts future falls. The knowledge gap has been identified and this thesis will seek to address these in subsequent chapters, starting with a description of the data sources and data acquisition process in Chapter 6.

Chapter 6: Data sources and measurement of multisite pain, falls and covariates

6.1 Overview

This chapter reviews the thesis' aims and objectives and describes the data sources required to address the knowledge gap highlighted by the systematic review and meta-analysis in Chapter 5. The measurements of multisite pain, covariates that may impact upon an association between pain and falls, and falls are then outlined and the chapter is summarised.

6.2 Revisiting this thesis' aims and objectives

The systematic review and meta-analysis described in Chapter 5 has identified knowledge gaps in the evidence examining the relationship between multisite pain and falls. The aims of this thesis therefore to address these knowledge gaps through the following objectives:

i) To describe the prevalence of self-reported falls, falls that require primary health care attendance and falls that require hospital admission in a population-based sample of community-dwelling older people;

ii) To test the hypothesis that older people with multisite pain are more likely to experience a future self-reported fall than older people with no pain;

iii) To test the hypothesis that older people with multisite pain are more likely to seek primary health care for a future fall than older people with no pain;

iv) To test the hypothesis that older people with multisite pain are more likely to be admitted to hospital as a result of a future fall than older people with no pain.

Addressing these hypotheses requires specific data on pain, covariates and falls and this information is not contained in a single database. Therefore, multiple data sources are required and these must then be linked at an individual level to enable analyses. Each data source will now be described in turn, and a time frame for the study period including each data source is summarised.

6.3 Data sources

6.3.1 The North Staffordshire Osteoarthritis Project (NorStOP)

NorStOP is a population based observational cohort study whose primary objective was to determine the course and prognosis of pain syndromes and the impact of these syndromes on participation and health care use (Thomas et al, 2004). The project consists of three linked population based surveys, named NorStOP1, NorStOP2 and NorStOP3, whose sampling frame comprises all individuals aged 50 years and over who were registered to receive care from one of eight general practices in North Staffordshire, United Kingdom. The study was approved by the North Staffordshire Research Ethics Committee; the Local Research Ethics Committee reference numbers are 05/Q2604/20 for NorStOP1,

05/Q2604/72 for NorStOP2 and 06/Q2801/90 for NorStOP3. Full details of study design and methodology have been published by Thomas et al (2004).

Participants were mailed two surveys, a General Health questionnaire and a Further Pain questionnaire to complete if pain in the hand, hip, knee or foot was reported. These surveys were accompanied by a letter from the GP practice and a study information leaflet explaining that the research was being conducted to ensure the local health economy was providing the 'right type of services'. Participants were informed that the purpose of the study was to 'find out how many people suffer from joint pain in the local population'; no specific mention of other factors, including falls, was made. Participants were asked if they consented to medical record review and those who did were recorded as consenters in the study database. Reminders were sent to non-responders after two and four weeks. The same surveys were sent again at 3 year and 6 year follow up with similar non-responder reminders. NorStOP1, NorStOP2 and NorStOP3 all followed the same methodology and their survey waves dates are displayed in table 6.1. Note that NorStOP3's second follow up is 7 years due to clinics overrunning (this follow up will however continue to be referred to as 'six year follow up' to encompass each NorStOP cohort's final follow up wave). The NorStOP study population is described further in Chapter 7.

Table 6.1 NorStOP survey: dates of baseline, three and six year follow up

	NorStOP 1	NorStOP 2	NorStOP 3
Baseline survey	April 2002	July 2002-August 2003	February 2004 – April 2005
Three year follow up	April 2005	October 2005-September 2006	February 2007 – April 2008
Six year follow up	April 2008	January 2009 – December 2009	July-August 2011*
*=7 year follow up			

6.3.2 General practice medical records

Each baseline survey respondent who consented to medical record review has linked data available from their general practice consultations. Information is extracted from general practice consultations by a Health Informatics team, linked to survey responses by a unique survey identifier and stored in a consultation database. The general practice consultation database contains information including reason for consultation, diagnosis and treatments including medication. The medical record data extends to the end of the three year survey wave for three year non-responders or respondents who stopped consenting at three year follow up. For non-responders of the six year follow up, responders who withdrew consent at 6 year follow up and respondents who consented and completed six year follow up, the medical record data extends to the end of the six year follow up period. Figure 6.1 provides a timeline of the dates described.

Primary Care clinical coding was developed in the late 1960s when Dr John Perry wrote the Oxford Medical Information System (OXMIS), based on the International

Classification of Diseases Eighth Revision (ICD-8) (Benson, 2011). This system became widely used in general practice as computers became integrated into clinical practice. This system was largely superseded by the READ code nomenclature, developed in the early 1980s by Dr James Read (Benson, 2011). This code is based on the International Classification of Diseases version 9 (ICD-9) (for diagnoses), although Dr Read himself developed codes for symptoms, examination findings, preventative care and investigation results, among others (Benson, 2011).

The READ codes are organised in a hierarchy, with groups of codes separated into chapters. Each code of the 5-Byte coding system contains 5 characters (or bytes); the addition of each character makes the code increasingly more specific. The codes are divided into 'chapters' according to groups of diseases, symptoms, laboratory findings and so on. Table 6.2 demonstrates the hierarchical system of 5-Byte READ codes, as extracted from the Clinical Terminology Browser Version 3 (NHS Information Authority, 2011).

Table 6.2 An example of the READ code 5-byte hierarchy used in GP consultations to code consultations in general practice

Level	**Descriptor**	**Characters**
Level 1	Circulatory system diseases	G….
Level 2	Ischaemic heart disease	G3…
Level 3	Angina pectoris	G33..
Level 4	Angina decubitus	G330.
Level 5	Nocturnal angina	G3300

The GP consultation records used in this study contain the 5-byte coding system, both the full 5 character code and the chapter heading (for example using table 6.2, the record would contain a chapter heading G and the full code G3300).

6.3.3 Prescription records

The GP consultation records also contain detailed information about prescriptions. This information is extracted by an informatics team, linked with the NorStOP survey data using a unique survey identifier and stored in a separate database to the GP consultations given the enormous amount of data. The information in the prescription database includes the medication name and the corresponding chapter code in the British National Formulary (BNF), for example 'naproxen' and Chapter 10.1.1 (Joint Formulary Committee, 2014).

6.3.4 Hospital Episode Statistics (HES)

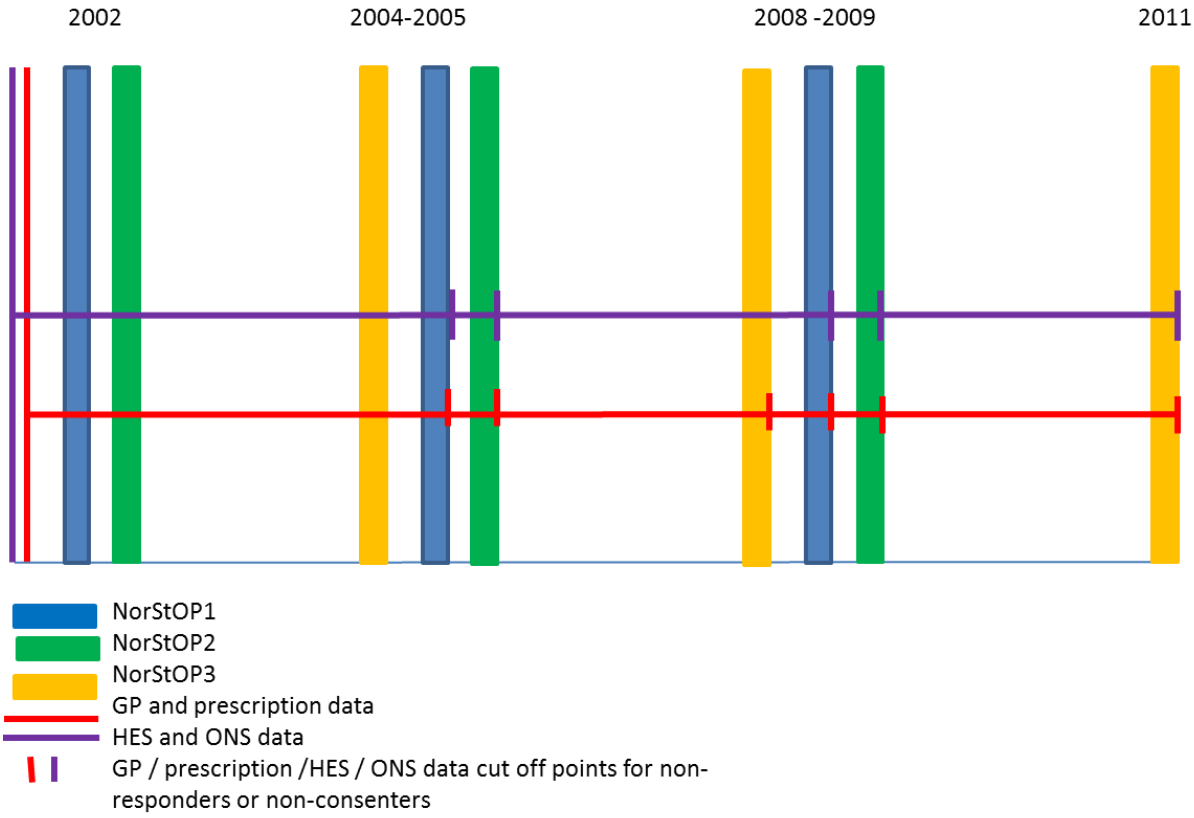
HES is a comprehensive records based system that contains identifiable patient information from all NHS Trusts in England (NHS Information Centre, 2010). Two HES data sources were requested from the NHS Information Centre; the Admitted Patient Care (APC) dataset and the Accident and Emergency (AE) dataset. In this thesis only the APC database could be used for analysis as it was not possible to extract information about specific diagnoses from the AE dataset. The APC database uses two different coding systems to record information in a standardised fashion. The International Classification of Disease version 10 (ICD-10), which superseded ICD-9 in 1995, is used to record information relating to diagnosis, for example cause of admission and diagnosis. The Office for

Population, Censuses and Surveys: Classification of Interventions and Procedures version 4 (OPCS-4) is used to record details of any procedures or interventions performed, for example hip replacements. Information about falls and fall-related injuries is extracted from the HES APC dataset. Data was requested from the NHS Health and Social Care Information Centre (NHSIC) from 1st January 2002 through to 31st December 2012 inclusive.

6.3.5 Office for National Statistics mortality data

The Office for National Statistics (ONS) dataset contains identifiable patient information on cancer incidence and cause of death as detailed on the death certificate (Office for National Statistics, 2010), and is a reliable method of determining occurrence, date and cause of death. Data was requested from the NHSIC 1st January 2002 through to 31st December 2012 inclusive. The time line for the data collection of each data source is depicted in figure 6.1.

Figure 6.1 A time line depicting data collection for each of the data sources



6.4 The data linkage process

The NorStOP survey data, GP consultation records, prescription records, HES and ONS data were linked using individual level identifiable data sent to the NHSIC. Permission to undertake this data linkage was obtained from the Secretary of State for Health under Section 251 of the NHS Act 2006 because NorStOP responders had not provided consent for this specific use of their identifiable data (postcode, NHS number, date of birth, sex). In reality, this process took 18 months; Appendix 5 provides an in-depth analysis of the ethical and legal aspects of using identifiable data for secondary research purposes without consent; this includes details of a literature review to explore the evidence around this challenge and a Patient and Public Involvement exercise which informed the basis of the

application for the correct approvals. Appendix 6 contains study approval documentation from the Local Research Ethics Committee and the Ethics and Confidentiality Committee ran by the National Information Governance Board.

6.5 Selecting covariates to include in analysis

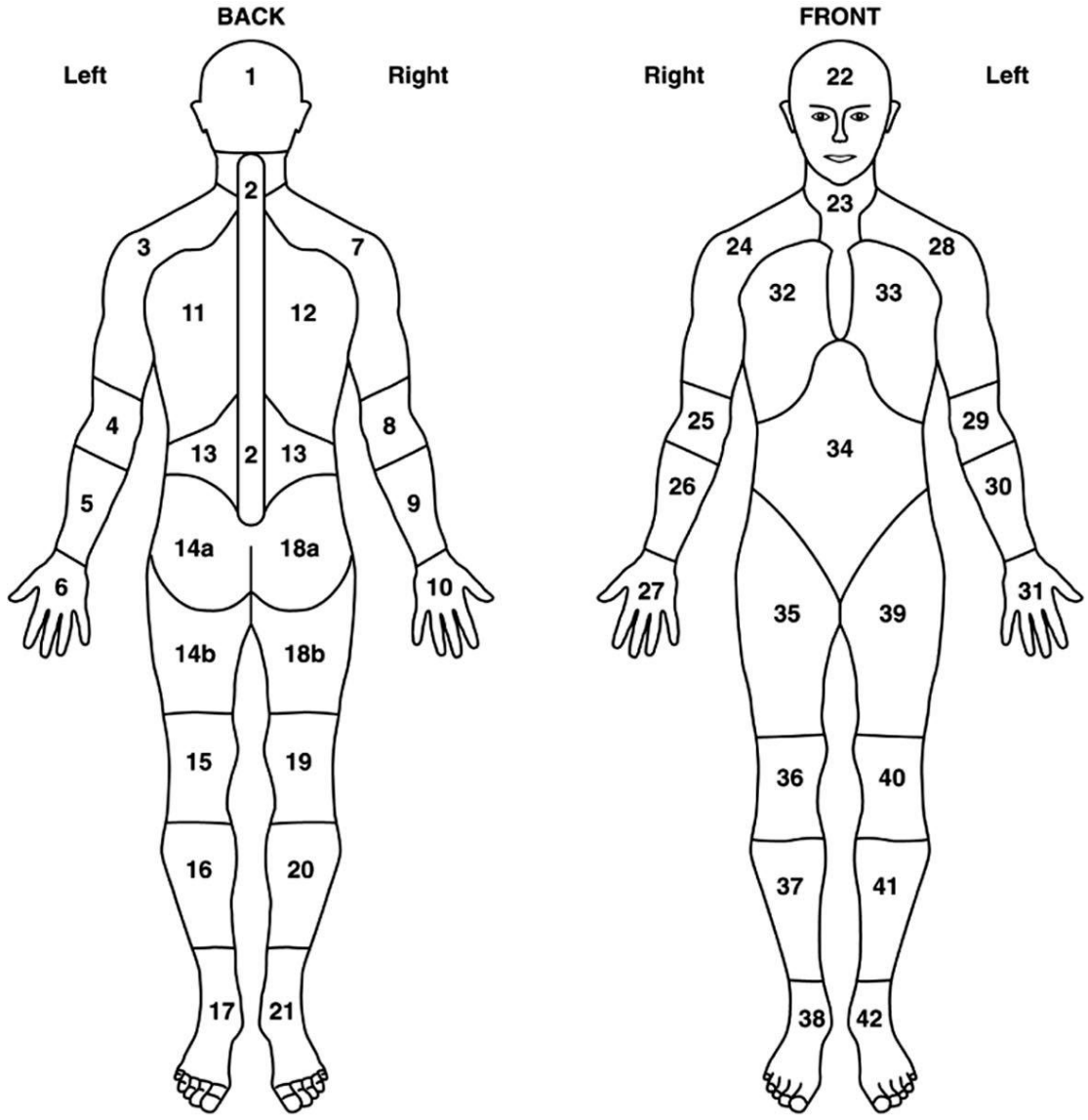
Once the data sources had been established and the availability of potential confounders or influencers of the pain-falls relationship confirmed, the covariates were selected based on the evidence presented in Chapter 4 and upon those that had been measured by studies included in the systematic review (Chapter 5). The next section describes the measurement of all the variables included in analysis: pain, potential confounders and influencing factors (called 'covariates' in this thesis) and falls.

6.6 Measurement of the independent variable: pain

6.6.1 Data collection and survey tool

Information relating to pain was derived from the NorStOP General Health Questionnaire at baseline, three year follow up and six year follow up. Participants were asked, as a screening question, whether they had 'experienced any pain, lasting at least one day, during the past month'. A yes or no response was recorded. Those replying positively were asked to indicate the site(s) of their pain in a body manikin as demonstrated in figure 6.2 (Lacey et al, 2005). The body manikin records 44 discrete anatomical areas. Participants were asked to include 'any ache, discomfort or stiffness' in their consideration of pain and were asked to exclude pain caused by feverish illness and menstrual pain.

Figure 6.2 The body manikin used in the NorSTOP survey to measure pain



Body manikins are often used as a screening instrument to estimate the prevalence of pain in selected body areas (Lacey et al, 2005). Lacey et al (2005) found a high degree of inter-rater reliability when scoring completed manikins and a high degree of consistency in the classification of widespread pain between multiple raters. For example, eight trained non-clinical staff were asked to score completed manikins and complete scoring agreement among all raters ranged

from 78% to 100% (kappa>0.60) with 98% complete agreement over the presence or absence of widespread pain (kappa = 0.98) (Lacey et al, 2005).

6.6.2 Classification of pain

Using the manikin data, pain will be classified using two different measures:

i) A continuous measure of the total number of pain sites, from 0-44

ii) A measure of the spread of pain (henceforth termed 'widespreadness')

6.6.2.1 Number of pain sites

The number of pain sites is a simple count of the number of shaded areas on the manikin, as coded by the NorStOP survey team using a standard transparent template overlaying the completed manikin. Participants who answered 'no' to the pain screening question and then went on to shade the manikin (n=75) or those who answered 'yes' to the pain screening question and did not shade any areas on the manikin (n=211) were classified as inconsistent pain responders. Those respondents with such discrepancies were excluded from the analysis to ensure that the pain measure was consistent across all participants. The number of pain sites is measured on a continuous scale from 0 to 44.

6.6.2.2 Widespread pain

Widespread pain is defined as pain that affects multiple (including non-joint) sites in the body (McBeth et al, 2014). It is used in this thesis to explore the relationship between more extensive pain phenotypes and falls. Here widespread pain was classified according to the criteria included in the American College of

Rheumatology (ACR) criteria for fibromyalgia (Wolfe et al, 1990). These criteria require participants to have pain above and below the waist, on the right and left sides of the body and in the axial skeleton (McBeth et al, 2010). Using the ACR definition of widespread pain to classify respondents' pain moves beyond a simple count of painful body sites towards a classification that carries with it connotations of chronic widespread pain syndromes such as fibromyalgia. At the severe end of the 'pain spectrum', using widespreadness as a measure may reveal stronger associations with falls than using a simple continuous measure of pain sites, since widespread pain has been associated with poorer psychological health, fatigue and sleep disturbance (Hunt et al. 1999), factors which may potentially increase the risk of falls.

For this thesis, widespread pain scores ('no pain', pain but not widespread pain termed 'some pain', 'widespread pain') were generated. To do this, each respondent had a binary code generated for reporting the presence or absence of pain in the right upper limb, left upper limb, right lower limb, left lower limb and axial skeleton. Next, the codes were combined to identify respondents who meet the ACR criteria for widespread pain (those who reported pain in the left upper limb, right lower limb and axial skeleton or those who reported pain in the right upper limb, left lower limb and axial skeleton). Finally, respondents who reported pain in the pain screening question and who shaded the manikin but who didn't meet the criteria for widespread pain are coded as a distinct group 'some pain' and those who stated they had no pain and did not shade the manikin are grouped as 'no pain'. Although abdominal pain was excluded from the widespreadness measure, it is included in the 'some pain' grouping. Thus, widespreadness was analysed using three categories: 'widespread pain', 'some pain' and 'no pain'.

6.7 Covariate measurements

6.7.1 Potential confounding factors

The association between pain and falls may be altered by confounding factors. A confounding factor (also termed 'confounding variable' or 'confounder') is a variable that is correlated either directly or inversely to both the dependant variable and the independent variable; a confounder must affect or predict the risk or rate in the unexposed (referent) group, and not be affected by the exposure or the outcome (Rothman et al, 2008). For example, the socio-economic status of respondents may act as a confounder since there is an association between pain and lower socio-economic status, and socioeconomic status might influence the risk of falls. Thus socio-economic status may explain any observed association between pain and falls rather than the pain itself. Importantly, socio-economic status and other confounding variables are not in the causal pathway between pain and falls i.e. having pain does not directly influence socio-economic status, which in turn directly affects the risk of falls. A variable that may plausibly appear on the causal pathway between pain and falls is considered as a 'mediator' of the relationship between pain and falls and this is discussed below.

Reviewing the evidence presented thus far, the potential confounders of the association between pain and falls considered in this thesis' analyses are age, sex and socioeconomic position. Table 6.3 presents the potential confounders, data source and measurement; a brief discussion of the measures of age and socio-economic position now follows.

Table 6.3 Potential demographic confounders, their data sources and measurement

Potential confounder	Data source	Measurement
Age	General practice consultation records	Continuous measure Categorical measure (categories split 5 yearly)
Sex	General practice consultation records	Categorical: female / male
Socio-economic position	NorStOP questionnaire & Index of Multiple Deprivation indicator	Categorical data

6.7.1.1 Age

The United Nations defines older people as those aged 60 years and older (United Nations, 2017). However, the systematic review and meta-analysis reported in chapter 5 found researchers used different age limits in their studies of older people; the majority of studies including adults aged 65 years and older, some studies included adults aged 70 years and older (for example Leveille et al, 2009) and some studies included adults aged 50 years and older (for example Hayashibara et al, 2010). This thesis uses a population of adults aged 50 years and older. Whilst this population may be younger than traditional convention as described by the UN definition of older people, 50 years is used as the youngest age in order to capture to falls experiences of those transitioning into later life over the duration of this longitudinal study.

6.7.1.2 Socio-economic position

Socio-economic position includes constructs around the individual and groups within the structure of society. For example, an individual's education level is constrained by educational opportunities available within society and according to family circumstances (Galobardes et al, 2007). Measures of socio-economic position therefore include constructs relating to the individual (for example, educational attainment, income, occupation, wealth) and to the area (for example, deprivation indices). Area level indicators are useful when individual level data is not available and can serve as a proxy to individual level socioeconomic position, however the potential for measurement bias arising from giving all individuals the same score must be considered and bias resulting in underestimating or overestimating an effect size has been reported (Davey-Smith et al, 1998; Subramanian et al, 2006; Geronimus, 2006). The most commonly used proxy indicator for area level socio-economic position in the UK for small areas is the Index of Multiple Deprivation (IMD). 'Small areas' are generated by the Office for National Statistics as a standard way to divide the UK into areas of approximately 1500 residents (Department for Communities and Local Government, 2016). The IMD combines information from seven domains that are weighted to produce an overall relative measure of deprivation. In order of weighted proportion, the domains are income, employment, education, health deprivation and disability, crime, barriers to housing and services, and living environment deprivation (Department for Communities and Local Government, 2015). A score is derived from the individual's postcode and then categorised into quintiles ranging from most deprived to least deprived. As demonstrated above, socio-economic status may well be a confounding factor in the association between pain and falls; it must

therefore be taken account of to ensure a measure of the independent effect of pain on falls in obtained. Composite measures of socio-economic status are acceptable in this situation, as the researcher is aiming to control the effects as a confounder rather than looking specifically at the relationship between falls and socio-economic status (Galobardes et al, 2007).

It is recognised that socio-economic position has the potential to change over the life course as one moves through childhood and parental influences through to working age and into retirement. Thus, the present thesis uses the IMD as an area-level indicator and educational attainment, occupation and an income measure as individual indicators over the life course. Educational attainment is a long-established facet of individual socio-economic position and is easy to measure in self-administered questionnaires (Galobardes et al, 2007); it can be viewed as measuring the transition from childhood socio-economic position into an individual position (Galobardes et al, 2007). There is some evidence that lower levels of education are associated with reduced risk of falling as found in a statistically significant relationship by Barrett-Connor et al (2009) and again in a non-significant trend by Deandrea et al (2010). This might be possibly explained by those with lower levels of educational achievement being more likely to be in manual jobs and therefore be more physically active and thus less likely to fall. The present study uses educational attainment as measured in NorStOP, in which participants were asked whether they had attended full time education or university after leaving school; with dichotomous yes / no responses and an unsure category subsequently coded in the NorStOP database.

Occupational status is another traditional measure of individual socio-economic position. The NorStOP survey derived classifications from the Office for National

Statistics (2000) and the Office for National Statistics (2002) (categories are (1) higher managerial and professional, (2) lower managerial / professional, (3) intermediate occupations, (4) self-employed, (5) lower supervisory/ technical, (6) semi-routine, (7) routine; these categories were subsequent collapsed to form non-manual (including (1) through (5) and non-manual work (6) and (7)).

Income and wealth are indicators that most directly measure material circumstances (Lynch & Kaplan, 2000). The NorStOP survey team developed a question to capture the concept of income, although this has not been repeated in future epidemiological surveys to date. Taken in combination with other SEP indicators, income is a useful addition to measure socio-economic position, notwithstanding the possible challenges of changeable income and the inverse causality effect whereby those with ill health have reduced earning potential and thus lower incomes, rather than lower income being a cause of poorer health (Galobardes et al, 2007). Table 6.4 summarises the measures used in the present thesis.

Table 6.4 Measures of socio-economic position in this thesis' study

Measure	Derivation	Categories
Educational attainment	Did you go from school to full-time education or university? Yes / No	Yes /No / Unknown
Income	Thinking about the cost of living as it affects you, which of these descriptions best describes your situation: i) find it a strain to get by from week to week; ii) have to be careful with money; iii) able to manage without much difficulty; iv) quite comfortably off	Adequate / Inadequate / Unknown
Occupational status	What is your current employment status? i) Employed; ii) Not working due to ill health; iii) retired; iv) unemployed / seeking work; v) housewife; vi) other If working, what is your job title (examples are factory worker, welder, office worker, shop assistant, lawyer)? If you are not working, or are retired, what was your last job title?	Manual / Non-manual / Unknown
Index of Multiple Deprivation IMD)	Post code of respondent, confidentially matched to IMD indicator	Least deprived / 2nd least deprived / middle quintile / 2nd most deprived / most deprived

6.7.2 Established falls risk factors and additional potential influencing covariates

In addition to potential confounders, other covariates that might influence the relationship between pain and falls must be considered in order to reflect 'real life' and be clinically meaningful. Therefore, traditional falls risk factors and other potential influencers of the pain-falls relationship must be measured and taken account of. Table 6.5 presents a summary of the potential influencing covariates selected to include in the thesis' analysis along with their data source and measurements. Those variables whose measurements require an explanation beyond that provided in table 6.5 are now discussed.

6.7.2.1 Multimorbidity

Multimorbidity was measured using the Charlson Comorbidity Index (CCI), a measure that takes into account the number and seriousness of co-morbid conditions to predict all-cause mortality at one year (Charlson et al, 1987; Khan et al, 2010). The CCI has been validated in different populations (Khan et al, 2010) and has been shown to be a valid summary co-morbidity measure for use in epidemiological studies to predict an outcome (Austin et al, 2015). Using a weighting system to acknowledge that certain conditions are more problematic than others (for example, diabetes with microvascular and macrovascular complications including visual problems, peripheral neuropathy and renal impairment requiring multiple medications is scored higher than diabetes with no complications) means the CCI is more reflective of 'real life' than a simple morbidity count; the potential for misclassification bias is also minimised, for example where one respondent may score 2 on a simple morbidity count with end stage chronic obstructive pulmonary disease and peripheral vascular disease requiring surgery and another may score 2 with hypertension and squamous cell

carcinoma of the skin completely excised, yet the morbidities in the former scenario have a much more serious life impact.

The CCI considers 16 diagnostic categories and each category is allocated a weight, for example ‘metastatic tumour’ carries the highest weight of 6, and mild liver disease carries the lowest weight of 1; appendix 7 provides disease categories and their weightings. Each respondent is scored according to the presence of the listed diagnostic categories as indicated by the READ codes in their medical records. Extracting the data from the general practice consultation records to ensure all relevant diagnostic READ codes were included was a complex undertaking, a summary of which is provided in 7; the list of READ codes used to extract information is available upon request from the thesis’ author VW. The CCI scores range from 0-33 (the highest score within the thesis samples was 8). The measure was treated categorically, with categories of 0, 1-2 and 3-8 respectively dichotimised at the mean value excluding 0.

6.7.2.2 Cognitive impairment

Cognitive impairment is an established risk factor for falls in national guidelines (for example the NICE guidelines on falls prevention (NICE, 2013)). Muir et al (2012) confirmed this statistically significant increased risk in their systematic review and meta-analysis of cognitive impairment in falls risk. The NorStOP survey used the alertness behaviour subscale (ABS), one of the twelve dimensions of the validated Sickness Impact Profle (SIP) (Bergner et al 1981) to measure cognitive ‘complaint’ rather than ‘impairment’. The components of the ABS-SIP are found in appendix 8 and include yes /no responses to questions

about multitasking, minor accidents, reaction times, task completion, problem solving, orientation, forgetfulness, attention span, mistakes and concentration skills. Each question is weighted and summed to provide an overall score, ranging from 0 to 100. The ABS-SIP score is analysed both on a continuous scale and categorically using 0 as no cognitive complaint, 1-14 as mild cognitive complaint, 15-38 as moderate cognitive complaint and 39-100 as severe cognitive complaint; this is based on even categories of non-zero scores with 33% of respondents in each category, as used by Westoby et al (2009). The thesis will henceforth use the term cognitive 'complaint' rather than 'impairment', although recorded difficulties with each of the ABS-SIP score components is also indicative of cognitive impairment, defined by the 'symptomatic pre-dementia stage on the continuum of cognitive decline, characterised by objective impairment in cognition that is not severe enough to require help with the usual activities of daily living' (Langa & Levine, 2014).

6.7.2.3 Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression scale (HADS) (Zigmond & Snaith, 1983). The HADS has a high degree of validity for anxiety and depression case finding and for assessment of symptom severity and performs well in a variety of settings including primary care (Bjelland et al, 2002). Here, the HADS anxiety and depression subscales are used as continuous measures (range 0-21) with the mean HADS score for both subscales explored within the different pain groups. The HADS is also considered a categorical variable using the following cut off points: 0-7 in respective subscales are considered normal, 8-10 are considered borderline and 11 or over indicates clinical 'caseness' of either anxiety or depression (Snaith, 2003).

6.7.2.4 Medication

Medications are prescribed using the electronic system in primary care and are therefore very likely to appear in medical records. There may be occasions where a GP has hand-written a prescription and not updated the records accordingly but, from experience, these are likely to be rare events and are most likely to be one-off prescriptions for analgesia or antibiotics. This information is captured in the general practice prescription records as detailed above and uses codes according to chapters defined in the BNF. The chapter codes are then searched for each respondent for the three months prior to baseline survey return date, or in the three months prior to three year follow up where necessary. Three months prior was determined through clinical experience; most repeat prescriptions are prescribed either monthly or two monthly, therefore to use prescriptions from only a month prior would potentially miss repeat prescribing on a two-monthly basis.

Each respondent will have a total count of different medication generated. The different medication is captured by using BNF sub-chapters and identifying the same medications to ensure they are only counted once (for example, a repeat prescription of ramipril appearing three times in the dataset will only be counted once, and a similar but not identical medication (for example candesartan) will be counted as a separate medication).

6.7.2.4.1 Total medication count

The mean number of the total medication count was used to compare pain groups.

6.7.2.4.2 Analgesic use including NSAIDs

In the UK, there are more than 300 different analgesic preparations available for GPs to prescribe (Joint Formulary Committee, 2013), and many different compounds of similar strengths. A system is therefore required to group similar analgesics together and streamline the database. Given the mixed evidence about analgesic use presented in Chapter 4, particularly for narcotic (or opiate) medication, the present thesis aims to identify the maximum strength of analgesic a respondent has been prescribed and use this as the variable to ensure analgesic use is taken account of in analysis. Such a classification system was developed by Bedson et al (2013), who derived a heriarchical analgesic categorisation according to equipotency across medication classes (Bedson et al, 2013; Ndlovu et al, 2014). Using sub-chapter codes from the BNF, medications were coded according to the following groups:

0) No analgesics
1) Basic analgesics
2) Weak combination opioids
3) Moderate combination opioids and opioids
4) Strong combination opioids and opioids
5) Very strong single opioids

NSAID use was coded as a separate variable to enable analysis of NSAID use separately to other analgesic use.

Analgesic use was defined as prescriptions for analgesia in the three months prior to baseline survey return date or in the three months prior to three year follow up where necessary. The highest numerical category (the strongest analgesic

category) was taken to represent analgesic use in respondents. Those who had no prescriptions in that time period were coded as 'no analgesic use'. Over the counter medication cannot be accounted for within this data set, so it is possible that some respondents classified as 'no analgesic use' were self-administering over the counter medication from group 1, which may lead to misclassification bias and underestimation of the impact of medication on falls risk. NSAID use was also defined in the three months prior to baseline survey completion. A separate variable for NSAID use was generated to ensure that, as a group '6' drug in the original hierarchy developed by Bedson et al (2013), the highest numerical category would not supersede the preceding opiate categories and therefore exclude opiate use from analysis.

6.7.2.5 Physical functioning

Physical functioning is measured in NorStOP using the Medical Outcomes Study SF-36 Physical Functioning scale (MOS-SF 36), with the ten separate items and an overall component score (Thomas et al, 2004; Ware & Sherbourne,1992) being available for analysis. The single item "Does your health limit you in walking 100 yards?" was selected to extract information about physical functioning as this item was found by Mottram et al (2008) and the NorStOP survey team to measure the most severe level of mobility limitation; Bohannon et al (2004) also previously used this single item to measure mobility limitation. Moreover, combining items from the physical functioning subscale of the MOS-SF-36 to give an overall score has been demonstrated to be mathematically flawed, since some of the items are ordinal in nature and thus cannot be combined unless transposed into interval data (Muller

et al, 2009; Merbitz et al, 1989; Wright, 1989). Finally, missing data is evident in the physical functioning items within NorStOP; the question assessing ability to walk 100 yards has the least amount of missing data (0.8% missing compared to 1.6% for an item relating to climbing stairs and 3.6% missing when the ten items are combined).

For this thesis, physical functioning is measured using the single item question regarding walking for 100 yards and is analysed as ordinal data with outcomes corresponding to "no, not limited", "yes, limited a little" and "yes, limited a lot".

Table 6.5 Summary of covariate measurements and the data source from which they were derived

Potential influencing variable	**Data source and derivation**
Multimorbidity	General practice consultation records
Dizziness	NorSTOP survey: have you experienced 'dizziness or unsteadiness' over the past three months? Yes or no
Poor hearing	NorStOP survey: have you 'suffered from deafness?' Yes / no
Poor vision	NorStOP survey: 'have you had problems with eyesight (excluding the need for glasses)?' Yes or no
BMI	Height and weight as recorded by NorStOP respondents in the survey
Depression	NorStOP survey HADS depression subscale
Anxiety	NorSTOP survey HADS anxiety subscale
Cognitive impairment	NorStOP survey ABS-SIP
Total medication count	General practice prescription records: Total number of medications from different BNF chapters prescribed
Maximum strength analgesia	General practice prescription records: Most potent opioid-based analgesic prescribed
NSAID use	General practice prescription records: Prescription of NSAID yes/ no
Physical functioning	NorStOP survey MOS SF36 Physical Component Scale
Previous history of fall	NorStOP baseline survey self-reported fall
HADS = Hospital Anxiety and Depression Subscale; ABS-SIP = Alertness Behaviour Subscale-Sickness Impact Profile; MOS SF36= Medical Outcomes Study SF36	

6.8 Falls

6.8.1 Self-reported falls

Information on self-reported falls is gathered from the NorStOP survey, which asked respondents to report any falls they had experienced in the three months prior to questionnaire completion using the following question:

"Thinking back over the past 3 months, have you suffered from any of the following?

a. *a fall or falls …"*

The question was repeated in the same format at three year follow up and six year follow up and required respondents to answer 'yes' or 'no'.

6.8.2 Falls requiring primary health care utilisation: GP-recorded falls

There is a paucity of literature exploring the use of fall-related codes in general practice and the literature to date focuses on using falls data recorded in HES data or collected directly from the patient. As such, there are no examples from which to draw to aid the decision over which codes to use to ensure maximum capture of falls; a pragmatic approach based on clinical experience is therefore adopted. Information about GP-recorded falls is extracted from the general practice medical records using READ codes. The NHS Clinical Terminology Browser (NHS Information Authority, 2011), an interactive computer programme that contains all READ codes in use in clinical practice was searched for READ codes pertaining to falls. The codes found are listed in table 6.6.

Table 6.6 Fall related READ codes that are used to extract GP-recorded falls status

5 byte READ code	Meaning
16D..	Falls
16D1.	Recurrent falls
16D2.	Number of falls in the last year
16D3.	Does not fall
16D4.	No fear of falls
16D5.	Fall onto outstretched hand
U10..	[X] Falls
U100.	[X] Fall on same level involving ice and snow
U101.	[X] Fall on same level from slipping, tripping and stumbling
U102.	[X] Fall involving ice-skates skis roller-skates or skateboards
U103.	[X] 0th fall same level due collision/ pushing by another person
U104.	[X] Fall while being carried or supported by another person
U105.	[X] Fall involving wheelchair
U106.	[X] Fall involving bed
U107.	[X] Fall involving chair
U108.	[X] Fall involving other furniture
U109.	[X] Fall involving playground equipment
U10A.	[X] Fall in and from stairs and steps
U10B.	[X] Fall on / from ladder
U10C.	[X] Fall on and from scaffolding
U10D.	[X] Fall from, out of or through building or structure
U10E.	[X] Fall from tree
U10F.	[X] Fall from cliff
U10G.	[X] Diving / jumping into water causing injury other than drowning or submersion
U10H.	[X] Other fall from one level to another

U10J. U10z.	[X] Other fall on same level [X] Unspecified fall
TC… TC0.. TC1.. TC2.. TC3.. TC4,, TC5,, TC6.. TC7.. TCy.. TCz..	Accidental falls Fall on or from stairs or steps Fall on of from ladders or scaffolding Fall from our out of building or other structure Fall into hole or other opening in surface Other fall from one level to another Fall on same level from slipping, tripping or stumbling Fall on same level– collision/push/shove by/ with other person Fracture, cause unspecified Other falls Accidental falls NOS

As table 6.6 demonstrates, to search using a three-byte READ code might include codes that are not relevant and thus introduce misclassification bias. For example, the code U10G. (diving or jumping into water) is not related to the falls under investigation in this thesis, yet would be included as fall if ‘U10’ was searched. Each of the 4byte codes in the table were searched to ensure that irrelevant codes would not be captured and none of these 4-byte codes appeared in the dataset. Thus, information on falls was extracted from the GP consultation data using the three-byte codes ‘16D’ and ‘U10’ and the two byte code ‘TC’.

To ensure that no codes were missing from the extraction strategy, academic GPs working within the research centre were asked to provide a list of READ codes that they used to code falls within their consultations. All seventeen GPs replied with a combination of the codes listed above; no additional codes appeared. All of the GPs highlighted that their most frequent coding practice for consultations

involving a fall were to code either the cause of the fall (for example, ‘urinary tract infection’ of ‘dizziness’) or the consequences of the fall (for example, (pain in the back, knee or lower limb, or soft tissue injuries). The implications of this coding practice are discussed at length in the discussion sections of the relevant analysis chapter.

It is possible that multiple fall-related codes are generated on the same day by a patient attending the GP, then seeing the practice nurse for a wound dressing. A search of the dataset revealed no falls codes on the same date for the same respondent. Some respondents had multiple fall-related codes entered over a short time period, for example over a two-week period. Since these may represent frequent fallers or falls that resulted in an injury requiring frequent attendance (for example, frequent dressings of a pretibial laceration), it was decided that, due to uncertainty, these consultations were coded as new ‘falls’.

Two falls measurements are taken from the GP consultation records: i) the number of respondents who have a fall (any fall) recorded in their GP consultations ii) the total number of falls for each respondent.

6.8.3 Falls requiring secondary health care utilisation: HES-recorded falls

HES APC data uses ICD-10 codes to record diagnosis or cause of admission in up to twenty different data fields. The ICD-10 was searched to obtain fall-related codes to use to extract fall-related codes from the HES data. Table 6.7 presents all ICD10 fall-related codes. Not all these codes are relevant to the thesis, for example W02 (fall involving ice-skates, skis, roller skates or skateboards) is not likely to be relevant to the study population.

Referring to the published literature does not provide a consensus view on which ICD-10 codes should be used to extract out falls coded in HES-APC data. Annual reports published by NHS Data (for example the Monthly HES summaries from April 2012-February 2013) provide summaries of falls data including total number of falls and falls admissions rates. This data does not distinguish specific type of fall and includes all the codes above (NHS Digital, 2017). The most common codes for falls were 'unspecified' [W19] (36.2%), 'falls on the same level through slipping, tripping and stumbling' [W01] (21.8%) and 'other fall in the same level' [W18] (12.7%) NHS Digital, 2017). Other studies using HES data to measure falls or fall-related injuries have used ICD10 codes W00-W19 and excluded codes that suggest work-related injuries, for example W12 (fall from scaffolding) (Gilbert et al, 2010). In their analysis of unintentional falls in older people in the UK, Scuffham et al (2003) used W01, W05, W06, W07, W08, W09, W10, W18 and W19.

Taking a pragmatic approach based upon Scuffham's (2003) work, W09 (fall from playground equipment) is excluded due to the pathophysiological mechanism resulting in that kind of fall is unlikely to be representative of the pathophysiology of the falls explored in this thesis (i.e those related to ageing, frailty, dizziness, sarcopaenia amongst other reasons) and W17 is included (fall from one level to another) as a possible code used by healthcare professionals to capture fall from a pavement to the road, or down a step, both of which could be falls arising from the factors under examination in this thesis. The HES falls codes used in this thesis are therefore: W01, W05, W06, W07, W08, W10, W17, W18 and W19 (as indicated by * in table 6.7).

Table 6.7 ICD-10 Codes used to extract fall-related information from secondary care admission data (HES)

HES code/ ICD-10	Code name
W00	Fall on same level involving ice and snow
W01*	Fall on same level from slipping, tripping and stumbling
W02	Fall involving ice-skates, skis, roller-skates or skateboards
W03	Other fall on same level due to collision with, or pushing by, another person
W04	Fall whilst being carried or supported by others e.g. being accidentally dropped while being carried
W05*	Fall involving wheelchair
W06*	Fall involving bed
W07*	Fall involving chair
W08*	Fall involving other furniture
W09	Fall involving playground equipment
W10*	Fall on and from stairs and steps including fall on or from escalator, incline, involving snow and ice on stairs and steps, ramp
W11	Fall from ladder
W12	Fall from scaffolding
W13	Fall from, or out of or through building or structure (includes fall from balcony, bridge, building, flag-pole, floor, railing, roof, tower, turret, viaduct, wall, window) (excludes collapse of a building or structure, fall or jump from burning structure)
W14	Fall from tree
W15	Fall from cliff
W16	Diving or jumping into water causing injury other than drowning or submersion including striking or hitting again bottom when jumping or diving, wall or diving board of swimming pool, water surface
W17*	Other fall from one level to another including fall from or into cavity, cherry picker, dock, haystack, hole, lifting device, mobile elevated work platform, pit, quarry, shaft, sky lift, tank, well
W18*	Other fall on the same level including fall from bumping against object, from or off toilet, on same level NOS
W19*	Unspecified falls including accidental fall NOS
*codes that are used to extract falls information in the thesis	

It is possible that some patients will receive more than one HES falls code within a 24-hour period. This can be generated through admissions to different wards, each generating their own set of associated codes to enable correct payment for services. For example, a patient may fall and fracture their hip and be admitted on a 'fractured neck of femur' pathway under the care of orthopaedics on an admissions unit, then have their operation and go through to recovery, then be transferred to a temporary ward bed on a general surgical ward whilst waiting for an orthopaedic bed, thus generating four different admission episodes. Duplicate dates relating to fall codes were identified and duplicate entries were excluded from the total falls count.

Thus, two HES-fall outcomes were recorded: i) number of respondents who have ever had a HES-recorded fall ii) the total number of HES-recorded falls for each respondent.

6.9 Summary

This chapter has restated this thesis' aims and objectives and described the data sources that were required to undertake analysis. Selection of covariates have been described and measurements of the independent variable (pain), the dependent variable (falls) and covariates to be accounted for in analysis due to their impact on any association between pain and falls have been presented. The next chapter will provide a summary of the NorStOP study population, describe how the study samples used in this thesis are derived and compare the thesis study samples to local and national statistics.

Chapter 7: NorStOP and the thesis study samples

7.1 Introduction

This chapter presents a summary of the NorStOP study and describes the processes through which the baseline NorStOP study sample was obtained. The samples used in this thesis (named thesis sample A and thesis sample B) to address the hypotheses are derived from the NorStOP baseline population and this process is explained with a study flow chart and presentation of inclusion and exclusion criteria. Thesis samples A and B are then assessed descriptively for risk of bias. A comparison is made with NorStOP baseline, local and national populations. Next, bias due to non-response and to other respondent losses at baseline is explored. Finally, bias from study attrition is considered and a chapter summary is provided.

7.2 Deriving the NorStOP sample

The NorStOP sampling frame consisted of 26,705 adults aged 50 years and older who were registered at eight different general practices in North Staffordshire, as identified by the Keele GP Research Network.

Before mail out, GPs were asked to screen out people with severe psychiatric or terminal illness so that they could be excluded from the survey mail out. This occurred before baseline surveys for NorStOP1, NorStOP2 and NorStOP3. After exclusions, 26,625 people were mailed the NorStOP surveys and accompanying information. Further exclusions were undertaken during the mailout process as

events including unknown addresses and deaths became apparent. Table 7.1 provides a summary of the sampling frame, drop outs and subsequent survey response rates. The total number of people eligible to partake in the NorStOP surveys was therefore 26,129.

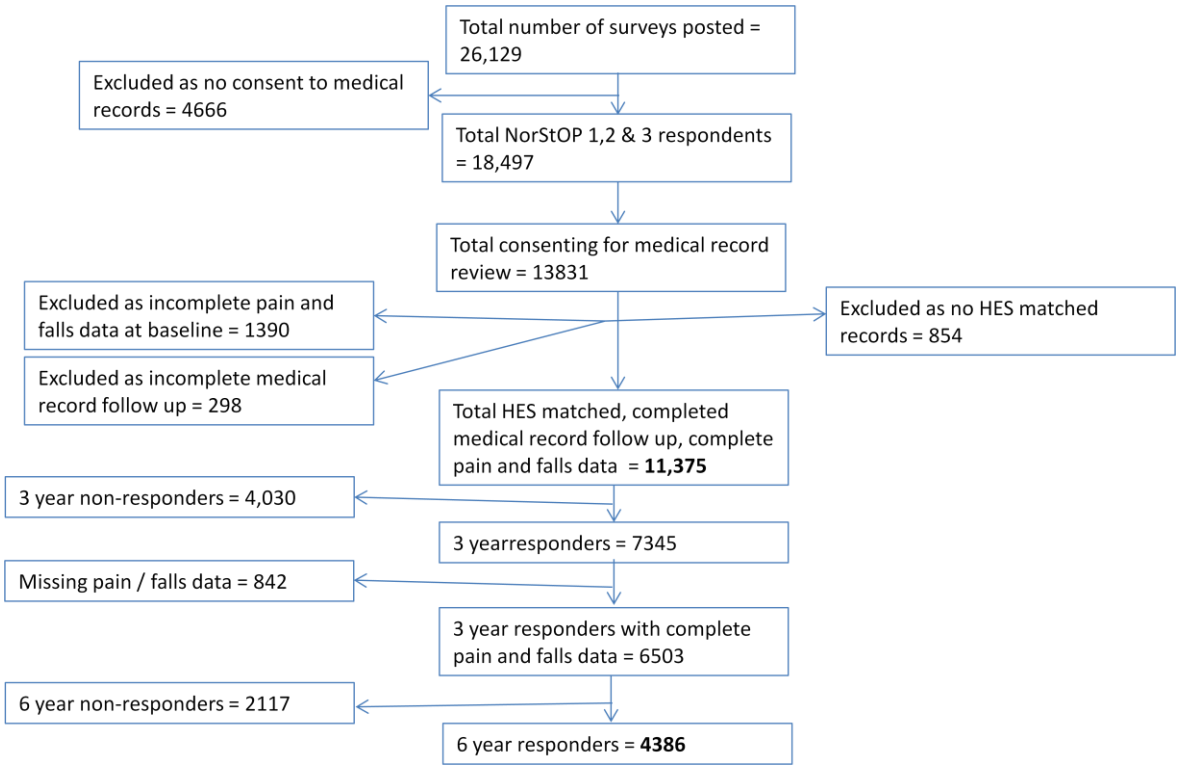
Table 7.1 NorStOP: Summary of the sampling frame, drop outs and baseline survey response rate

	Total	**NorStOP1**	**NorStOP2**	**NorStOP3**
Number identified	26,705	11,309	8,984	6,412
Excluded prior to mailing	80	79 *55 deaths and departures* *24 on GP screen*	0	1 1 death
Number eligible for mailout	26,625	11230	8984	6411
Excluded during mailing	496	175 *45 deaths and departures* *25 withdrawals* *105 returns addressee unknown*	221 *98 deaths and departures* *28 withdrawn (19 ill and 9 ineligible)* *95 returned addressee unknown*	100 *43 deaths and departures* *16 withdrawn (4 ill, 12 ineligible)* *41 returned addressee unknown*
Eligible baseline health survey population	26,129	11055	8763	6311
Responders	18,497	7,878 (71.3%)	6,108 (69.7%)	4,511 (71.5%)
Non-responders/ refusals	7632	3177 109 ill health 255 refused 2813 non-response	2655 83 ill health 223 refused 2349 non-response	1800 49 ill health 1589 refused 162 non-response

7.3 Deriving the thesis study sample

Starting with NorStOP responders (n=18,497), figure 7.1 charts respondent flow through the study and into the final samples used for analysis in this thesis. Consent to medical record review was provided by 13,831 respondents and their survey responses were linked with their general practice consultation and prescription records.

Figure 7.1 Thesis study population flow chart: from responding to NorStOP baseline survey to end of six year follow up



NorStOP consenters (n=13,831) had their information sent to the NHSIC as detailed in Chapter 6 to link HES and ONS data. 854 identifiers were returned with unmatched records; these respondents were subsequently excluded from analysis. Data for the general practice consultation and prescription databases were still being extracted as the thesis started and so the 298 NorStOP

respondents who did not have complete general practice consultation and prescription records were excluded from analysis. Exclusion criteria were therefore unmatched HES or ONS records and incomplete general practice consultation or prescription records.

Inclusion criteria were based upon responses to the two pain questions in the NorStOP survey: a) have you experienced any pain, lasting at least one day, during the past month? (yes or no response); and b) Indicate the site(s) of pain by shading the body manikin (shading or no shading response). Respondents were included if they:

i) Answered ‘yes’ to the pain screening question and shaded the manikin
ii) Answered ‘no’ to the pain screening question and did not shade the manikin

Respondents who answered ‘yes’ to the pain screening question but who did not shade the manikin, and those answering ‘no’ but proceeded to shade the manikin were excluded from analysis since their answers were nonsensical and it was not possible to infer which answer represented the true pain experience. Respondents who provided incomplete responses to the pain questions were also excluded; thus 1390 exclusions were made due to incomplete or inconsistent pain responses.

A total of 2158 respondents were therefore excluded due to unmatched HES and ONS records, incomplete general practice and prescription data and incomplete or inconsistent pain responses; there are respondents who fulfilled more than one exclusion criteria, hence the number 2158 does not equate to simple addition of numbers in each exclusion category. 11,375 respondents were therefore included

in this thesis' analyses to examine the prevalence of self-reported, GP and HES-recorded falls. This sample (n=11,375) was also used to measure the relationship between pain and future GP and HES recorded falls. The sample of 11,375 respondents will now be termed thesis sample A.

As demonstrated in figure 7.1, 7,345 of the 11,375 respondents completed three year follow up and, of those, 6503 respondents continued to be included in this thesis' study sample due to their complete and consistent answers to the pain questions described above; 842 respondents were excluded due to incomplete or inconsistent pain answers in their three year follow up survey. 4386 respondents remained in the study at six year follow up after 2117 failed to return their survey. The sample consisting of 4386 respondents who have three and six year follow up with complete pain data is referred to as thesis sample B, this sample (n=4386) will be used to examine the relationship between multisite pain and self-reported falls.

This thesis will therefore undertake analyses using two samples. Both sample A and B contain information on pain and covariates for 11,375 respondents all taken at the baseline survey time point, i.e. the pain measures and self-reported covariates are derived from the baseline NorStOP survey and covariates extracted from general practice consultations and prescriptions are derived during the three months prior to the baseline NorStOP survey distribution date for each NorStOP cohort. The larger size of sample A (n=11,375) compared with sample B (n=4386) means risk estimates using the larger sample A are closer to the true population risk because there are more individual values from which an average estimate can be formed, thus sample A will be used to address examine falls prevalence and the relationship between pain and future GP and HES-recorded fall. The

relationship between multisite pain and self-reported falls will be examined using thesis sample B (n=4386) since this contains complete follow up information and is therefore less at risk of bias from missing data.

7.4 Assessing the thesis samples for risk of bias

Before analyses are undertaken, it is prudent to assess risk of bias within the thesis samples A and B since this may impact upon the validity of results. This thesis aims to address the hypotheses using a cohort of respondents who have been followed up over a six year period. Cohort studies have potential sources of bias including the choice of sampling frame and subsequent sample representativeness compared to local and national figures, non-response to surveys and attrition from follow up. In this thesis, additional potential sources of bias come from differences between those who consented to medical record review and those who did not, those who had incomplete or inconsistent pain responses and those who did not, and those who had unmatched HES, ONS or general practice or prescription records and those who did not . These risks will now be assessed in the sections that follow.

7.4.1 Representativeness of the thesis samples A and B compared to NorStOP, local and national populations

The purpose of this thesis is to provide evidence to GPs and policy makers to ensure that pain experience is taken into account when assessing and managing falls risk in older people, if a link is found. Therefore, the results of this thesis must be generalisable to a wider population. To enable to results to be generalisable,

this thesis' study population must be representative of the wider population, for example the eligible baseline health survey population, the local Staffordshire population and the national English population. This section will now compare basic demographic information within thesis study samples A (n=11,375) and B (n=4386), the NorStOP eligible health survey population, local (Staffordshire) census data and national (England) census data.

7.4.1.1 Age and sex distributions

Table 7.2 provides a breakdown of age distribution in England, Staffordshire, the eligible NorStOP population and thesis samples A and B and table 7.3 provides the age and sex distributions of England, Staffordshire, the NorStOP eligible population and thesis samples A and B.

Table 7.2 The age distribution of national and local populations, the NorStOP eligible population and the thesis' study samples A (n=11,375) and B (n=4386)

Age (years)	England (2001 census) %	Staffordshire (2001 census) %	NorStOP eligible population %	Thesis sample A %	Thesis sample B %
50- 54	21.1	21.9	15.7	14.1	18.1
55 - 59	17.3	18.7	19.4	18.6	22.7
60 - 64	14.9	15.4	15.0	15.6	18.7
65 - 69	13.4	13.3	13.8	16.0	18.0
70 -74	12.0	11.8	12.2	13.4	12.0
75- 79	10.0	9.4	10.4	11.3	7.4
80- 84	6.5	5.8	7.7	7.2	2.5
85 - 89	3.4	2.8	3.8	2.9	0.6
90 +	1.4	1.1	2.0	1.0	0.0

Table 7.3 Age and sex distributions of national and local populations, the NorStOP eligible population and thesis study samples A (n=11,375) and B (n=4,386)

Age (years)	England (2001 census)		Staffordshire (2001 census)		NorStOP eligible population		Thesis sample A		Thesis sample B	
	% Male	% female	% male	% female	% male	% female	% male	% female	% male	% female
50-54	49.6	50.4	50.3	49.7	50.2	49.8	45.3	54.7	43.3	56.7
55-59	49.5	50.5	49.9	50.1	50.2	49.8	48.3	51.8	44.1	55.9
60-64	49.1	50.9	50.3	49.7	50.2	49.8	49.7	50.3	47.7	52.3
65-69	48.0	52.0	48.6	51.4	48.3	51.7	49.6	50.4	48.5	51.5
70-74	45.5	54.5	45.9	54.1	43.8	56.2	46.1	53.9	45.0	55.0
75-79	41.8	58.2	42.2	57.8	42.6	57.4	45.0	54.9	46.9	53.1
80-84	37.0	63.0	36.7	63.3	35.5	64.5	38.6	61.4	37.9	62.2
85-89	30.4	69.6	29.9	70.1	30.0	70.0	33.5	66.5	42.8	57.1
90-94	23.5	76.5	23.0	77.0	21.2	78.8	23.6	76.4	0.0	100.0
95-99	18.8	81.2	17.8	82.2	15.9	84.1	36.4	63.4	--	-
100 +	20.3	79.7	26.8	73.2	0.0	100.0	-	-	-	-

The NorStOP eligible population is generally representative of Staffordshire and England populations although there are a slightly higher proportion of women in the oldest old age group compared to local and national figures. Thesis samples A and B have more men included in the oldest old categories than would be expected from local and national census projections. The NorStOP eligible population has a lower proportion of adults aged 50-54 years old and a higher proportion of adults aged 55 years and older compared to the local and national population. This difference is seen in thesis sample A until aged 85 years and older, where there are fewer of the oldest old in thesis sample A than in the local and national samples. Thesis sample B has even fewer respondents aged 75 years and older than the local and national samples. This reduction in proportion

of the oldest old within thesis sample A and B is likely due to attrition due to advancing age and ailing health, with only the fittest older people remaining in the study of the six year follow up; this is known as the healthy cohort effect and is discussed throughout the thesis, particularly in Chapter 12.

7.4.1.2 Occupational class

Table 7.4 presents occupational class distribution across England, Staffordshire and thesis samples A and B, as defined in the Office for National Statistics (2000 and 2002). This information is not available for the NorStOP eligible study population.

Table 7.4 Distribution of occupational class in national and local population and thesis study samples A (n=11,375) and B (n=4,386)

Occupational class	England %	Staffordshire %	Thesis sample A %	Thesis sample B %
1 Higher managerial and professional	5.8	5.8	6.0	7.1
2 Lower managerial and professional	13.5	13.6	13.0	16.7
3 intermediate occupations	6.4	5.8	11.3	13.3
4 self-employed	7.8	8.0	6.2	6.2
5 lower supervisory / technical	5.3	6.0	6.0	5.7
6 Semi-routine	9.3	9.8	22.7	24.1
7 Routine	7.8	8.9	27.4	22.1
8 Retired / not working /inadequate title/ student / voluntary work	1.6	1.6	0.8	0.66
9 unclassified	42.6	40.3	6.5	4.1

The key difference between thesis samples A and B and the local and national figures lies in the 'unclassified' occupations. The census information has a higher percentage of 'unclassified' occupations, perhaps as a result of misclassification of semi-routine and routine jobs that have a higher proportion in thesis sample A and B.

7.4.1.3 Respondent distribution across participating general practices

Table 7.5 shows the percentage of respondents from each of the eight general practices from which the NorStOP study population were sampled.

Table 7.5 The distribution of GP practices that provided the NorStOP sample within the NorStOP eligible population and thesis sample A (n=11,375) and B (n=4386)

General practice	NorStOP eligible population %	Thesis sample A %	Thesis sample B %
A	13.9	16.6	19.0
E	10.3	9.5	8.4
H	13.9	14.3	13.8
I	19.3	18.9	19.1
L	8.9	8.2	8.6
M	13.7	12.7	12.0
N	6.9	7.7	8.5
P	13.0	12.2	10.7

The highest proportion of survey responders come from practices I and A and the lowest proportions are derived from practices L and N. Although the distribution of practices follows a similar pattern in the NorStOP eligible population and thesis

samples A and B, a greater percentage of respondents in thesis samples A and B are from general practice A and there are fewer respondents from general practice P in the thesis sample B.

7.4.1.4 Ethnicity

Staffordshire has very little ethnic diversity; 98.6% of adults aged 50 to 54 years and 99.5% of adults aged 90 years and older are recorded as 'white' in the 2001 Census. The NorStOP population is therefore representative of Staffordshire with more than 99% of respondents self-reporting their ethnicity as 'white'. This is not completely representative of England, where 94.9% of 50 to 54 year olds and 98.6% of adults aged 90 years and older were recorded as 'white'. There is thus a difference is ethnicity structure in the youngest age groups of older people in England, although ethnicity of the oldest age groups is close to the NorStOP study population, this must be taken into account when interpreting this thesis' results.

7.4.1.5 Sample representativeness: summary

In summary, when compared to local and national populations, there are fewer of the oldest old in both thesis sample A (n=11,375) and B (n=4386), and this is more marked in thesis sample B. There are more semi-routine and routine occupations in the thesis samples A and B when compared England and Staffordshire figures and there is a preponderance for more respondents to be registered at a particular general practice than in the NorStOP eligible population. Thesis samples A and B entirely reflect the ethnicity of the Staffordshire population, although this local population is not representative of England for adults aged 50-54 years, where the proportion of adults self-identifying as 'white' is greater.

7.4.2 Risk of bias from respondent losses at baseline

7.4.2.1 Assessing non-response bias

Non-response bias, where groups of responders differ in characteristics to non-responders, is a potential source of bias that reduces a study's results validity. Basic demographic information about age and sex is available for non-responders to the baseline NorStOP survey and for those who were excluded during the mailout; these are now compared to the baseline NorStOP survey returners in table 7.6 and table 7.7.

Table 7.6 The age profile of the local population, the NorStOP mailout population and NorStOP responders and non-responders

Age group (years)	Staffordshire %	NorStOP mailout %	NorStOP responders %	NorStOP non-responders %
50-54	21.9	15.7	13.9	19.2
55-59	18.7	19.4	18.3	22.0
60-64	15.4	15.0	15.5	14.2
65-69	13.3	13.8	15.3	10.7
70-74	11.8	12.2	13.6	9.0
75- 79	9.4	10.4	11.3	8.4
80-84	5.8	7.7	7.7	7.9
85-89	2.8	3.8	3.3	5.0
90 +	1.1	2.0	1.2	3.7

Table 7.6 demonstrates that the NorStOP mailout sample contained fewer people aged 50-54 years compared to the general Staffordshire population. The non-responders were younger overall than the responders, with fewer people in the older age groups and more people in the younger age groups; correspondingly; the NorStOP responders had a smaller number of people aged 50-54 years compared with the mailout population and Staffordshire.

Table 7.7 Age and sex distribution of the local population, NorStOP mailout population , NorStOP non-responders and the NorStOP baseline study sample

Age group (years)	Staffordshire		NorStOP mailout		NorStOP non-responders		NorStOP baseline sample	
	% male	% female	% male	% female	% male	% female	% male	% female
50-54	50.3	49.7	50.2	49.8	58.3	41.7	45.2	54.8
55-59	49.9	50.1	50.2	49.8	55.6	44.5	46.9	53.1
60- 64	50.3	49.7	50.2	49.8	55.5	44.5	47.7	52.3
65- 69	48.6	51.4	48.3	51.7	52.7	47.3	46.8	53.2
70- 74	45.9	54.1	43.8	56.2	46.3	53.7	42.9	57.1
75- 79	42.2	57.8	42.6	57.4	41.6	58.4	42.8	57.2
80-84	36.7	63.3	35.5	64.5	30.7	69.3	37.2	62.8
85- 89	29.9	70.1	30.0	70.0	26.0	74.0	32.5	67.6
90- 94	23.0	77.0	21.2	78.8	21.9	78.1	21.1	79.0
95-99	17.8	82.2	15.9	84.1	12.3	87.7	30.0	70.0
100 +	26.8	73.2	0.0	100.0	0.0	100.0	0.00	0.00

As table 7.7 shows, a larger proportion of non-responders were men compared with both the local population and the NorStOP mail out population and this trend continued until aged 70 years old, when a larger proportion of women became non-responders compared to both Staffordshire and the NorStOP mailout population. The NorStOP baseline sample therefore had proportionally less men between ages 50 and 64 years than the NorStOP mailout sample and local population, although the oldest old categories had proportionally more women than the local population and NorStOP mailout comparison group. Overall, the age and profile of the NorStOP responders is not entirely reflective of that of Staffordshire, with the NorStOP responders generally older than the Staffordshire population. The sex profile is similar in the Staffordshire, responders and non-

responder samples and there are a greater proportion of women in most age groups within the NorStOP responder sample compared to the local population.

7.4.2.2 Assessing baseline drop-out risk of bias

NorStOP respondents were also excluded according to non-consent to medical record review, incomplete or inconsistent pain information, incomplete general practice consultation and prescription records and unmatched HES or ONS data. Tables 7.8 and 7.9 compare age and sex profiles for consenters, non-consenters and other excluded respondents with the initial NorStOP respondents the subsequently derived thesis sample A to investigate any systematic differences between groups and therefore risk of bias.

Table 7.8 Age distribution of NorStOP responders, consenters, non consenters and those included in thesis sample A

Age (years)	NorStOP responders %	NorStOP consenters %	NorStOP non-consenters %	Additional baseline drop outs %	Thesis sample A %
50- 54	13.9	14.2	13.0	14.7	14.1
55 - 59	18.3	18.6	17.2	17.6	18.6
60 - 64	15.5	15.5	15.5	14.3	15.6
65 - 69	15.3	15.9	13.6	15.1	16.0
70 -74	13.6	13.6	13.9	14.4	13.4
75- 79	11.3	11.2	11.8	11.3	11.3
80- 84	7.7	7.2	9.1	7.7	7.2
85 - 89	3.3	3.0	4.1	3.9	2.9
90 +	1.2	1.0	1.7	1.9	1.0
NorStOP respondents n=18,497; NorStOP consenters (those consenting to medical record review) n=13,381; NorStOP non-consenters (those not consenting to medical record review) n=4666; Additional baseline loss (no HES match, no complete medical record data or incomplete pain data) n=2158; Thesis sample A n=11,375					

Table 7.8 shows that the group who consented to medical record review was similar in age distribution to the NorStOP baseline survey population. A lower proportion of the non-consenter group were aged 50-54 years and the non-consenters had higher proportions of older age groups that the consenting group. The age profile of the consenters and the non-consenters is statistically significantly different, with the probability that they are the same calculated using a t-test as < 0.01. The additional baseline drop out group also contains a higher proportion of adults aged 70 years and older than the NorStOP respondent group. These differences are not carried into thesis sample A (n=11,375), which has an age profile generally matching the NorStOP responders and consenters.

Table 7.9 Age-sex distribution of NorStOP respondents, additional baseline drop outs and thesis sample A (n=11,375)

Age (years)	NorStOP respondents		NorStOP consenters		NorStOP non-consenters		Additional baseline loss		Thesis sample A	
	% male	% female	% male	% female	% male	% female	% male	% female	% male	% female
50-54	45.2	54.8	45.6	54.4	43.9	56.1	50.6	49.4	45.3	54.7
50-59	46.9	53.1	48.6	51.4	41.5	58.5	52.9	47.1	48.3	51.8
60-64	47.7	52.3	50.5	49.5	39.7	60.3	53.6	46.4	49.7	50.3
65-69	46.8	53.2	49.3	50.7	38.1	61.9	48.5	51.5	49.6	50.4
70-74	42.9	57.1	45.5	54.5	35.6	64.4	44.1	56.0	46.1	53.9
75-79	42.8	57.2	45.2	54.8	36.25	63.75	45.3	54.7	45.1	54.9
80-84	37.2	62.8	39.9	60.1	31.0	69.0	45.5	54.6	38.6	61.4
85 - 89	32.45	67.55	33.8	66.2	29.5	70.5	35.3	64.7	33.5	66.5
90 - 94	21.05	78.95	26.6	73.4	12.3	87.7	40.9	59.1	23.6	76.4
95 - 99	30.0	70.0	36.4	63.6	22.2	77.8			36.4	63.6
100 +										

NorStOP respondents n=18,497; NorStOP consenters (those consenting to medical record review) n=13,381; NorStOP non-consenters (those not consenting to medical record review) n=4666; Additional baseline loss (no HES match, no complete medical record data or incomplete pain data) n=2158; Thesis sample A n=11,375

Table 7.9 shows that the NorStOP baseline sample has proportionally more women than men in all age categories. The non-consenters had an even greater difference in proportions with more women than men dissenting from medical record review in all age groups. Men and women were more evenly distributed across the age groups in the additional baseline loss group. The impact of the marked non-response in women is to balance thesis sample A, with more equal groups of men and women until age 70 years, when a larger proportion are women in each subsequent age group, reflecting the NorStOP baseline sample.

Table 7.10 Education status, income adequacy and pain reporting in NorStOP respondents according to consent status, additional baseline drop outs and thesis sample A (n=11,375)

Variable	**NorStOP sample n=18497**	**NorStOP consenters n=13381**	**NorStOP non-consenters n=4666**	**Additional baseline losses n=2158**	**Thesis sample A n=11375**
FT education					
Yes (%)	2127 (11.5)	1633 (12.2)	443 (9.5)	255 (11.8)	1382 (12.2)
No (%)	15889 (85.9)	11454(85.6)	4046 (86.7)	1808(83.8)	9793 (86.1)
Missing (%)	481 (2.6)	294 (2.2)	177 (3.8)	95 (4.4)	200 (1.8)
Income adequacy					
Adequate (%)	9989(54.0)	7447 (55.7)	2291 (49.1)	896 (41.5)	6320 (42.7)
Inadequate (%)	8009(43.3)	5667(42.4)	2156 (46.2)	1189 (55.1)	4858 (55.6)
Unknown (%)	499 (2.7)	267(2.0)	219 (4.7)	73 (3.4)	197 (1.7)
Number of pain sites					
Mean (range)	9.5 (0-50)	9.6 (0-50)	9.0 (0-50)	3.8 (0-43)	6.1 (0-44)
SD	SD 8.4	SD 8.3	SD 8.5	SD5.5	SD7.2
Missing n (%)	6552 (35.4)	4120 (30.8)	1982 (42.5)	1390 (64.4)	0 (0)
Widespread pain					
No pain (%)	4736 (25.6)	3388 (25.3)	1376 (29.5)	321 (41.8)	3062 (27.6)
Some pain (%)	7252 (39.2)	5611 (41.9)	1596 (34.2)	343 (44.7)	5175 (45.5)
Widespread (%)	4201 (22.7)	3294 (24.6)	924 (19.8)	104 (13.5)	3138 (26.9)
Missing n (%)	2308 (12.5)	1088 (8.1)	770 (16.5)	1390 (64.4)	0 (0)

NorStOP consenters are those consenting to medical record review; NorStOP non-consenters are those not consenting to medical record review; Additional baseline loss are those with no HES match, no complete medical record data or incomplete pain data; Pain score calculated for the NorStOP sample, consenters and non-consenters by summarizing the number of pain sites if the screening question was answered as 'yes'; SD = standard deviation ; FT education = continuing education after aged 16 years

NorStOP non-consenters had a lower proportion of adults undertaking further education than consenters and the NorStOP baseline sample, as table 7.10 shows. The additional baseline losses group had a similar proportion of adults moving on to further education to the NorStOP baseline sample. The non-response and additional losses groups did not impact on the transition from NorStOP baseline survey group to thesis sample A as proportions in full time education remained similar overall.

There is a difference between consenters and non-consenters, with a greater proportion of consenters reporting income adequacy. The additional baseline losses group had the lowest proportion of respondents reporting income adequacy and these differences have a marked impact upon thesis sample A, where the difference in income adequacy is very different to the NorStOP baseline sample; 42.7% (6320 respondents) report income adequacy in thesis sample A compared to 54% (9989 respondents) in the NorStOP baseline sample. This difference must be considered in the context of other markers of socioeconomic status.

The prevalence of pain within thesis sample A (n=11,375) and B (n=4386) is presented and discussed in Chapter 8. It is also included briefly here to compare between samples to determine whether thesis sample A is fundamentally different in terms of pain reporting that the baseline NorStOP sample. The mean number of pain sites in the NorStOP baseline sample is 9.5 and is 6.1 in thesis sample A. This is obviously different and means that any effect measure relating to pain as derived from thesis sample A is likely to underestimate the true impact given that the number of pain sites is less. Rounded to a whole number, the difference in mean number of pain sites between consenters and non-consenters is 1; the consenters and non-consenters are therefore not fundamentally different in terms

of pain. The additional baseline loss group is very different, with a mean number of pain sites 4, quite different to the NorStOP sample mean of 10. This might be explained by the exclusion of respondents who did not complete the pain questions or did so inconsistently. Perhaps respondents assume that, by not shading the manikin, it is obvious that they don't have pain and therefore the pain screening question becomes superfluous. Therefore, more pain free respondents were excluded than those with pain, thus the mean number of pain sites for additional baseline losses is lower.

Widespread pain distribution follows a similar pattern to number of pain sites, with a much greater proportion of the additional baseline losses group reporting no pain when compared to the NorStOP baseline sample. NorStOP non-consenters had a lower proportion of widespread pain compared to consenters. Thesis sample A reported a greater proportion of all three categories compared to the NorStOP baseline population, although approximately one quarter of both samples reported widespread pain and some pain was the commonest category in each group. The greater proportion of all three pain categories in thesis sample A compared to NorStOP baseline is due to the missing data from the NorStOP baseline population; however thesis sample A broadly reflects the NorStOP baseline population.

7.4.2.3 Summary of bias risk due to respondent losses at baseline

NorStOP responders are generally older than the Staffordshire population, and there are proportionally more women in most of the age categories except ages 85-89 years and 95-99 years old, this difference may impact upon the generalisability of results to a population that does not have as high a proportion of

older people; this will be discussed in Chapter 12. Despite the differences in age profile within responders and non-responders, thesis sample A (n=11,375) follows a similar age structure to the NorStOP baseline sample. There are a greater proportion of women non-consenters compared to consenters yet the age-sex distribution of thesis A resembles the NorSTOP baseline sample such that risk of bias relating to age and sex from baseline additional losses is low. Educational attainment is similar in the NorStOP baseline sample and thesis sample A and so the risk of bias is low. Income adequacy distribution is very different across the groups and the pattern is reversed in thesis sample A, where income inadequacy more common than adequacy. This must be considered with other measures of socio-economic position and there is a potential for bias in this difference. The mean number of pain sites is lower in thesis sample A than the NorStOP baseline sample and any risk estimates relating to pain must consider this potential source of underestimation. The distribution of widespreadness is similar between the NorStOP baseline sample and thesis sample A.

7.4.3 Attrition through follow up

Loss of respondents during the follow up period, or attrition, can impact upon results if those that do not complete follow up are different to those who do. Table 7.11 shows that thesis sample B (n=4386) has a higher proportion of adults aged 50 - 69 compared to thesis sample A (n=11,375). This is due to natural attrition of older adults who have become increasingly frail or have died and are therefore unable to complete follow up surveys. This is reflected in the age distribution of the drop out group who have higher proportions of adults aged 70 years and older. The age-sex distribution (table 7.12) shows a higher proportion of men in the 65-89 year age groups compared with thesis sample A.

Table 7.11 Age distribution of thesis samples A (n=11,375) and B (n=4386) and baseline NorStOP responders who dropped out of follow up

Age group (years)	Thesis sample A n=11375	Drop outs n=6989	Thesis sample B n=4386
50 –54 (n, %)	1605 (14.1)	811 (11.6)	794 (18.1)
55- 59 (n, %)	2112 (18.6)	1117 (16.0)	995 (22.7)
60 –64 (n, %)	1771 (15.6)	952 (13.6)	819 (18.7)
65–69 (n, %)	1818 (16.0)	1030 (14.7)	788 (18.0)
70 –74 (n, %)	1521 (13.4)	997 (14.3)	524 (12.0)
75-79 (n, %)	1285 (11.3)	959 (13.7)	326 (7.4)
80 - 84 (n, %)	821 (7.2)	710 (10.2)	111 (2.5)
85 -89 (n, %)	325 (2.9)	297 (4.3)	28 (0.6)
90- 94 (n, %)	106 (0.9)	105 (1.5)	1 (0.0)
95-99 (n, %)	11 (0.1)	11 (0.2)	0 (0.0)
Drop outs are 3 year follow up non-responders or incomplete pain information			

Table 7.12 Age-sex distribution of thesis samples A (n=11,375) and B (n=4386) and baseline NorStOP responders who dropped out of follow up

Age (years)	Thesis sample A n=11375		Drop out between thesis sample A and B n=6989		Thesis sample B n=4386	
	Female (n, %)	Male (n, %)	Female (n, %)	Male (n, %)	Female (n, %)	Male (n, %)
50- 54	878 (54.7)	727 (45.3)	428 (52.8)	383 (47.2)	450 (56.7)	344 (43.3)
55 - 59	1093 (51.8)	1019 (48.3)	537 (48.1)	580 (51.9)	556 (55.9)	439 (44.1)
60 - 64	891 (50.3)	880 (49.7)	463 (48.6)	489 (51.4)	428 (52.3)	391 (47.7)
65 - 69	916 (50.4)	902 (49.6)	510 (49.5)	520 (50.5)	406 (51.5)	382 (48.5)
70 -74	820 (53.9)	701 (46.1)	532 (53.4)	465 (46.6)	288 (55.0)	236 (45.0)
75- 79	706 (54.9)	579 (45.1)	533 (55.6)	426 (44.4)	173 (53.1)	153 (46.9)
80- 84	504 (61.4)	317 (38.6)	435 (61.3)	275 (38.7)	69 (62.2)	42 (37.8)
85 - 89	216 (66.5)	109 (33.5)	200 (67.3)	97 (32.7)	16 (57.1)	12 (42.9)
90 - 94	81 (76.4)	25 (23.6)	80 (76.2)	25 (23.8)	1 (100.0)	0 (0.0)
95 -99	7 (63.6)	4 (36.4)	7 (63.6)	4 (36.4)		
100 +						

Lower levels of deprivation and satisfactory income adequacy are more prevalent in thesis samples A and B than and the drop out group (table 7.13), this is expected given the association of lower socio-economic position and poor health leading to study attrition.

Table 7.13 The distribution of socio-economic position indicators in thesis samples A (n=11,375) and B (n=4386) and respondents who dropped out of follow up

Variable	Thesis sample A (n=11375)	Drop out between thesis sample A and B (n=6989)	Thesis sample B (n=4386)
FT Education (n, %)			
Yes	1382 (12.2)	706 (10.1)	676 (15.4)
No	9793 (86.1)	6150 (88.0)	3643 (83.1)
missing	200 (1.8)	133 (1.9)	67 (1.5)
Income adequacy (n, %)			
Adequate	4858 (55.6)	3688 (45.2)	2632 (60.0)
Inadequate	6320 (42.7)	3157 (52.8)	1701 (38.8)
Unknown	197 (1.7)	144 (2.1)	53 (1.2)
IMD (n, %)			
Least deprived	2295 (20.2)	1332 (19.1)	963 (22.0)
2nd least deprived	2351 (20.7)	1327 (19.0)	1024 (23.4)
Mid deprived	2265 (19.9)	1385 (19.8)	880 (20.1)
2nd most deprived	2211 (19.4)	1411 (20.2)	800 (18.2)
Most deprived	2250 (19.8)	1532 (21.9)	718 (16.4)
missing	0.0	0.0	0.0
FT Education= continuing education after aged 16 years; IMD = Index of Multiple Deprivation			

The pain measures of thesis samples A and B and the drop outs is very similar (table 7.14). All groups have a mean number of pain sites of 6 and the widespread pain measures are almost identically proportioned in all three groups.

Table 7.14 The distribution of pain in thesis samples A (n=11,375) and B (n=4386) and respondents who dropped out of follow up

Variable	Thesis sample A (n=11375)	Drop out between thesis sample A and B (n=6989)	Thesis sample B (n=4386)
Number of pain sites Mean (range) standard deviation (SD)	 6.1 (0-44) SD 7.2 N=11,375	 6.1 (0-44) SD 7.3 N=6989	 6.0 (0-44) SD 7.0 N=4386
Widespread pain (n, %) No pain Some pain Widespread pain	 3138 (27.6) 5175 (45.5) 3062 (26.9)	 1919 (27.5) 3210 (45.9) 1860 (26.6)	 1219 (27.8) 1965 (44.8) 1202 (27.4)

In summary, attrition over follow up has the age and sex structure of thesis sample B compared with thesis sample A, with more men in the older age groups and fewer respondents aged 70 years and older in thesis sample B. Thesis sample B also has a greater proportion of respondents in the least deprived IMD categories. All of these differences can be explained by the healthy cohort effect whereby those in the poorest health are unable to continue in study follow up and the fitter 'survivors' populate the follow up cohorts. The pain measures are similar across thesis sample A, B and those who were lost to follow up, thus pain differences between groups is not likely to be a significant source of bias.

7.5 Chapter summary

This chapter has described in detail the derivation of thesis samples A and B in preparation for analyses. There is a risk of bias within the sample derivation and this must be considered when interpreting results, for example the NorStOP baseline study population are older and have proportionally more semi-routine and routine occupations in the sample than corresponding local and national populations. This impact is mitigated by responder losses at baseline and through NorStOP follow up which have resulted in thesis samples A and B having an age-

sex structure similar to local and national populations. The mean number of pain sites is lower in thesis samples A and B than the NorStOP baseline sample and any risk estimates associated with pain must be considered as potential underestimations. Having gained a clear understanding of the thesis sample development and the local and national context, the next chapter will describe the demographics and pain epidemiology of thesis samples A and B.

Chapter 8: Thesis study sample demographics and pain associations

8.1 Overview

This chapter describes the distribution of pain and covariates of thesis sample A (n=11,375, containing NorStOP baseline responders who consented for medical record review and who provided consistent responses to pain measures) and thesis sample B (n=4386, containing NorStOP respondents who completed all stages of follow up and provided consistent responses to pain measures), building on the detail from Chapter 7 which compared age, sex and socioeconomic position to local and national samples. The rationale for the chapter is explained and methods used to present information about pain and covariate distributions within thesis samples A and B are discussed. Covariate distributions across thesis samples A and B are presented and compared; this is followed by an analysis of pain distributions in thesis samples A and B and pain and univariate associations in thesis sample A. The results are discussed and implications for future analyses within this thesis are examined.

8.2 Rationale and chapter objectives

Pain and covariate distributions across thesis sample A and thesis sample B are presented to provide an overview of the demographic and health status of study respondents to set the scene for future analyses. Covariate distributions between thesis samples A and B are compared statistically to enable quantitative evaluation of the impact of drop out as respondents move between thesis sample

A and B; Chapter 5 (systematic review and meta-analysis) demonstrates why knowledge about respondent attrition is important to minimise risk of bias introduced through drop out. The covariate distributions between samples are therefore compared to enable clearer consideration of this potential source of bias.

Univariate associations between pain and covariates enable statistically significant relationships to be identified and thus have their impact considered during later analyses examining the relationship between pain and falls. For example, if depression is found to be highly correlated with pain status (either the number of pain sites or the widespread measure of pain), then any association between pain and falls found in this thesis may be, at least partly explained by the presence of depression. This is explained in greater detail in chapter 11, where the impact of putative influencers of the pain-falls relationship is discussed. It is important to know which covariates are associated with pain in this analysis so that due consideration is given in future analyses.

This chapter therefore seeks to:

i) describe the distributions of pain and covariates in thesis sample A and B, and quantify any differences;
ii) describe the univariate associations between covariates and pain measures

8.3 Methods

8.3.1 Presentation of pain and covariate distributions

Simple frequencies are used to describe the distribution of all covariates in thesis samples A (n=11,375) and B (n=4386).

8.3.2 Comparison of pain and covariate distributions between samples

8.3.2.1 Distribution of pain and covariates

The distribution of each continuous variable was measured and non-parametric distributions were confirmed. For example, the total medication count is skewed towards no medication, anxiety and depression scores are clustered towards the lower scoring end. Covariates that are expected to follow a normal distribution do not strictly exhibit this pattern; age is clustered between 50-60 years rather than the midpoint age in the sample range (75 years) and BMI is centred on 26.7kg/m^2, not the midpoint of the sample range 41.5 kg/m^2). Since continuous covariates are all distributed non-parametrically, non-parametric statistical tests are used in this analysis.

8.3.2.2 Comparison of mean values between groups

Continually distributed covariates have their mean values compared between thesis sample A and thesis sample B using the non-parametric Kruskal Wallis one-way analysis of variance (KW) test. The KW test (Kruskal and Wallis, 1952) is a multiple-sample generalisation version of a rank sums test that tests the hypothesis that several samples are from the same population (Stata, 2013). For example, in the context of this study considering the mean number of pain sites within thesis sample A and thesis sample B, the 'same population' would mean that all respondents with the same mean number of pain sites score would be in the same sample group. The test ranks the number of pain sites and corresponding thesis sample groups and assesses whether the same ranking would appear if the population was the 'same'. The result is given as a chi-squared calculation with an associated probability (*p)*, with a probability *(p*) of

<0.05 giving a statistically significant result, i.e. the populations are significantly different, or, in the example given, the number of pain sites varies significantly between thesis sample groups. The level of significance for the p-value is set at 0.05, a commonly used cut off point such that if the observed p-value is <0.05 it is considered good evidence that the null hypothesis can be rejected (Peacock & Peacock, 2010).

8.3.2.3 Comparison of categorical covariate distributions between samples

Comparison of categorical variable distributions between thesis samples A and B is done using the chi squared test. The chi squared test tests the null hypothesis that there is no association between the categorical variables by calculating expected frequencies and comparing these with observed values (Peacock & Peacock, 2010). Chi squared values are presented with an estimate of probability on how likely the result is to have been obtained if the variables are not associated, for example, how likely the differences in distribution are if there is no association with being in either thesis sample A or thesis sample B. A p-value of <0.05 means that the null hypothesis is rejected as the probably of this result occurring by chance alone in a situation where variables are not associated is less than 5%.

8.3.3 Pain and univariate associations

The association between the number of pain sites and categorical covariates is measured using the KW test since this involves a comparison of the mean number of pain sites across different categories.

The association between the number of pain sites and continuously distributed variables is done using the Spearman's rank correlation or the Kendall's tau, tests

that are used to measure the association between two continuously distributed non-parametric variables. Since there are ties within the data (for example, many respondents share the same number of pain sites and many respondents share the same anxiety score), Kendall's tau test is most appropriate (Peacock & Peacock, 2010). Kendall's tau test examines the null hypothesis that there is no tendency for one variable either to increase or to decrease as the other variable increases (Peacock & Peacock, 2010), for example that the number of pain sites does not change when depression score increases. The analysis program provides the tau-b estimate and a probability score (p-value). The test takes account of ranking value rather than the true value of the measurement and so the only conclusion that can be drawn is whether the association follows the null hypothesis, thus a p value < 0.05 means the null hypothesis (for example, that anxiety score and number of pain sites are independent) is rejected.

The association between the widespread pain measure (no pain / some pain / widespread pain) and categorically distributed covariates is measured using the chi squared test. The association between the widespread pain measure and continuously measured covariates is evaluated using the KW test.

Thesis sample A will be used to measure cross-sectional associations between pain and covariates since this is the larger sample that contains more data and will therefore provide estimates that are more representative of the wider population.

8.4 Results

8.4.1 Pain and covariate distributions in thesis sample A and thesis sample B

8.4.1.1 Age and sex

Table 8.1 provides a reminder of the age and sex distributions in thesis samples A and B. 50% (5701 respondents) of thesis sample A and 60% (2602 respondents) of thesis sample B are aged between 55 and 69 years of age. The mean age of thesis sample A is 65.9 years (SD 10.0, range 50 years to 99 years) and the mean age of thesis sample B is 62.9 years (SD 8.3, range 50 years to 90 years). There were 1263 (11%) adults aged 80 years and older in thesis sample A and 40 (3%) in thesis sample B. The age distribution between thesis sample A and B is statistically significantly different (p=<0.01).

Table 8.1. Age and sex distribution in thesis sample A and thesis sample B

Age (years)	**Thesis sample A n=11375**		**Thesis sample B n=4386**	
	Female (n, %)	Male (n, %)	Female (n, %)	Male (n, %)
50- 54	878 (54.7)	727 (45.3)	450 (56.7)	344 (43.3)
55 - 59	1093 (51.8)	1019 (48.3)	556 (55.9)	439 (44.1)
60 - 64	891 (50.3)	880 (49.7)	428 (52.3)	391 (47.7)
65 - 69	916 (50.4)	902 (49.6)	406 (51.5)	382 (48.5)
70 -74	820 (53.9)	701 (46.1)	288 (55.0)	236 (45.0)
75- 79	706 (54.9)	579 (45.1)	173 (53.1)	153 (46.9)
80- 84	504 (61.4)	317 (38.6)	69 (62.2)	42 (37.8)
85 - 89	216 (66.5)	109 (33.5)	16 (57.1)	12 (42.9)
90 - 94	81 (76.4)	25 (23.6)	1 (100.0)	0 (0.0)
95 -99	7 (63.6)	4 (36.4)		
100 +				

8.4.1.2 Socioeconomic position measures

Table 8.2 demonstrates approximately 50% of the respondents were employed in semi-routine or routine occupations in both samples (5704 respondents in thesis sample A and 2024 in thesis sample B). Approximately 85% of respondents had not gone on to full time education after completing schooling in both samples (9793 in thesis sample A and 3643 in thesis sample B) and income inadequacy was reported by 4858 respondents (42.7%) in thesis sample A and 1701 respondents (38.8%) in thesis sample B. Distribution across IMD quintiles showed more respondents in the least and second least deprived categories in thesis sample B compared with thesis sample A. All the socioeconomic position measures were statistically significantly different across samples.

Table 8.2 Socio-economic position indicators in thesis samples A (n=11,375) and B (n=4386)

Variable	Thesis sample A n (%)	Thesis sample B n (%)	Difference test of significance
Occupational class			
1 higher managerial and professional	683 (6.0)	313 (7.1)	p=<0.01
2 lower managerial and professional	1479 (13.0)	734 (16.7)	
3 intermediate occupations	1289 (11.3)	584 (13.3)	
4 self-employed	703 (6.2)	272 (6.2)	
5 lower supervisory / technical	685 (6.0)	249 (5.7)	
6 semi-routine	2587 (22.7)	1055 (24.1)	
7 routine	3117 (27.4)	969 (22.1)	
8 retired	1 (0.8)	0 (0.0)	
9 unclassified	831 (6.5)	210 (4.8)	
Full Time education			
Yes	1382 (12.2)	676 (15.4)	p=<0.01
No	9793 (86.1)	3643 (83.1)	
Unknown	200 (1.8)	67 (1.5)	
Income adequacy			
Adequate	6320 (55.6)	2632 (60.0)	p=<0.01
Inadequate	4858 (42.7)	1701 (38.8)	
Unknown	197 (1.7)	53 (1.2)	
IMD			
Least deprived	2295 (20.2)	963 (22.0)	p=<0.01
2nd least deprived	2351 (20.7)	1024 (23.4)	
Mid deprived	2265 (19.9)	880 (20.1)	
2nd most deprived	2211 (19.4)	800 (18.2)	
Most deprived	2250 (19.8)	718 (16.4)	
Unknown	3 (0.0)	1 (0.0)	

8.4.1.3 Physical health indicators

Table 8.3 presents the prevalence of physical health indicators within thesis samples A & B. 8471 respondents (74.5%) in thesis sample A and 3510 respondents (80.0%) in thesis sample B had a multimorbidity score of 0, indicating absence of any medical conditions included in the CCI. Approximately 15% of respondents had one included medical condition (1899 respondents in thesis sample A and 622 respondents in thesis sample B); 1005 respondents (8.8%) in thesis sample A and 254 respondents (5.8%) in thesis sample B had a CCI score of 2 or more. A quarter of thesis sample A (2809 respondents) reported dizziness, one fifth (2102 respondents) reported hearing impairment and one fifth (2359 respondents) reported visual impairment. The corresponding prevalence in thesis sample B were one fifth (873 respondents), 14% (631 respondents) and 15% (671 respondents) respectively. Mean BMI in thesis samples A and B was 27kg/m^2, indicative of an 'overweight' status. The differences between samples was statistically significant for all physical health indicators except BMI.

Table 8.3 The distribution of physical health indicators in thesis sample A (n=11,375) and B (n=4386)

Variable	Thesis sample A n (%)	Thesis sample B n (%)	Difference test of significance
Multimorbidity CCI			
0 (score 0)	8471 (74.5)	3510 (80.0)	p=<0.01
1 (score 1)	1899 (16.7)	622 (14.2)	
2 (score 2-8)	1005 (8.8)	254 (5.8)	
Dizziness			
Yes	2809 (24.7)	873 (19.9)	p=<0.01
No	8566 (75.3)	3513 (80.1)	
Hearing impairment			
Yes	2102 (18.5)	631 (14.4)	p=<0.01
No	9273 (81.5)	3755 (85.6)	
Visual impairment			
Yes	2359 (20.7)	671 (15.3)	p=<0.01
No	9016 (79.3)	3715 (84.7)	
BMI (kg/m^2) mean, SD	26.7 (11.9-71.5), 4.7	26.9 (15.1-71.5), 4.5	
Missing	416 (3.7%)	105 (2.4%)	p=0.15
CCI=Charlson Comorbidity Index; BMI = body mass index			

8.4.1.4 Mental health markers

As presented in table 8.4, the mean ABS-SIP score for cognitive complaint was 14.7 for thesis sample A and 11.5 for thesis sample B; the ABS-SIP score range is 0-100; both sample scores indicate a low average impact score. The mean Hospital Anxiety and Depression subscales scores for thesis sample A were 4.8 for depression and 6.7 for anxiety; corresponding means in thesis sample B were 4.1 and 6.5. Since a HADS score of between 0 and 7 on each subscale is considered within the normal range (Snaith, 2003). The sample mean experiences of depression and anxiety are within the normal range. The differences between groups were statistically significant for cognitive impairment and depression, but not for anxiety.

Table 8.4 The distribution of mental health indicators in thesis sample A (n=11,375) and B (n=4386)

Variable	Thesis sample A % (n given in cells)	Thesis sample B % (n given in cells)	Difference test of significance
Cognitive complaint Mean (range) Standard deviation Number in sample (%) Missing (%)	 14.7 (0-100) 23.4 10774 (94.7) 604 (5.3)	 11.5 (0-100) SD 19.9 4232 (96.5) 154 (3.5)	p=<0.01
Depression Mean (range) Standard deviation Number in sample (%) Missing (%)	 4.8 (0-21) 3.7 11120 (97.8) 255 (2.2)	 4.1 (0-21) 3.4 4311 (98.3) 75 (1.7)	p=<0.01
Anxiety Mean (range) Standard deviation Number in sample (%) Missing (%)	 6.7 (0-21) 4.2 11,110 (97.7) 265 (2.3)	 6.5 (0-21) 4.1 4311 (98.3) 75 (1.7)	p=0.15

8.4.1.5 Medication

The mean number of medications in both samples was 3 (see table 8.5). 23% (2,587) of thesis sample A had no medication prescribed in the three months prior to baseline NorSTOP survey and 763 (6.7%) of respondents had 10 or more medications prescribed. 1187 (27.0%) of thesis sample B had no medications prescribed and 154 respondents (3.5%) had 10 or more medications prescribed.

Approximately three-quarters of thesis samples A (8231 respondents) and B (3421 respondents) did not have paracetamol and / or opiate-based analgesia prescribed. Of those who did, 23.0% (1505 respondents) of thesis sample A and 24.0% (493 respondents) of thesis sample B had strong or very strong opioids prescribed. 10% of thesis sample A (1233 respondents) and thesis sample B (464 respondents) were prescribed NSAIDs. The difference in total medication count and pain medication prescriptions is statistically significantly difference between samples; this is not the case for NSAID medication.

Table 8.5 The distribution of medication measures in thesis sample A (n=11,375) and B (n=4386)

Variable	Thesis sample A (n=11,375)	Thesis sample B (n=4,386)	Difference test of significance
Total medication count Mean (range) SD	 3.5 (0-20) 3.5	 2.8 (0-20) 3.0	 p=<0.01
Pain medication maximum category 0 (n, %) 1 (n, %) 2 (n, %) 3 (n, %) 4 (n, %)	 8231 (72.3) 867 (7.6) 772 (6.8) 780 (8.9) 725 (6.4)	 3421 (78.0) 259 (5.9) 213 (4.9) 261 (6.0) 232 (5.3)	 p=<0.01
NSAID use Yes (n, %) No (n, %)	 1233 (10.8) 10142 (89.2)	 464 (10.6) 3922 (89.4)	 p=0.48
Pain medication maximum category: 0 No analgesics, 1 Basic analgesics, 2 Weak combination opioids, 3 Moderate combination opioids and opioids , 4 Strong combination opioids and opioids, 5 Very strong single opioids; SD = standard deviation; NSAID = non-steroidal anti-inflammatory			

8.4.1.6 Physical functioning

7928 respondents (69.6%) in thesis sample A and 3501 respondents (79.8%) in thesis sample B reported no difficulty walking 100 yards (table 8.5); 1378 respondents (12.1%) in thesis sample A and 281 respondents (6.4%) in thesis sample B reported a lot of difficulty walking 100 yards. The difference between samples is statistically significant.

Table 8.6 The distribution of physical functioning in thesis sample A (n=11,375) and B (n=4386) physical functioning

Physical functioning (difficulty walking 100 yards) n (%)	Thesis sample A	Thesis sample B	Difference test of significance
Yes, a lot	1378 (12.1)	281 (6.4)	p=<0.01
Yes, a little	1876 (16.5)	560 (12.8)	
No	7918 (69.6)	3501 (79.8)	
Missing	203 (1.8)	44 (1.0)	

8.4.1.7 Covariates: missing data

Variables obtained from general practice consultation and prescription records have no data missing and variables obtained exclusively from the NorStOP survey have some data missing. Education status, income, anxiety, depression, BMI and physical functioning have <5% of data missing therefore the impact of this missing data is therefore likely to be low. 604 respondents (5.3%) in thesis sample A did not complete the ABS-SIP scale and have missing data. This may impact on results if those with missing data all had a higher, or lower, level of cognitive impairment.

8.4.1.8 Pain and covariates: summary

Respondents in thesis samples A and B are from a range of ages and the proportion of males and females follows national trends. Thesis samples A and B contain a high proportion of semi-routine or routine occupations and the majority have not gone on to further education after leaving school; more respondents report income inadequacy than adequacy and this is also reported more frequently in thesis sample B. There are proportionally more respondents from the least deprived IMD groups in thesis sample B. Thesis sample B contains statistically significant lower proportions of physical health indicators and depression and cognitive impairment than thesis sample A and proportionally fewer medications and strong analgesics are prescribed in thesis sample B. The majority of both samples have no CCI-linked comorbidities, anxiety, depression and cognitive complaint measures in the 'normal' range and do not take analgesics. A greater proportion of respondents reporting no limitation in physical functioning are found in thesis B than thesis A. The differences between thesis samples A and B are largely explained by the 'healthy cohort' effect, whereby the healthiest people (i.e. those with least comorbidities, mental health difficulties and polypharmacy) remain in the cohort until the study ends.

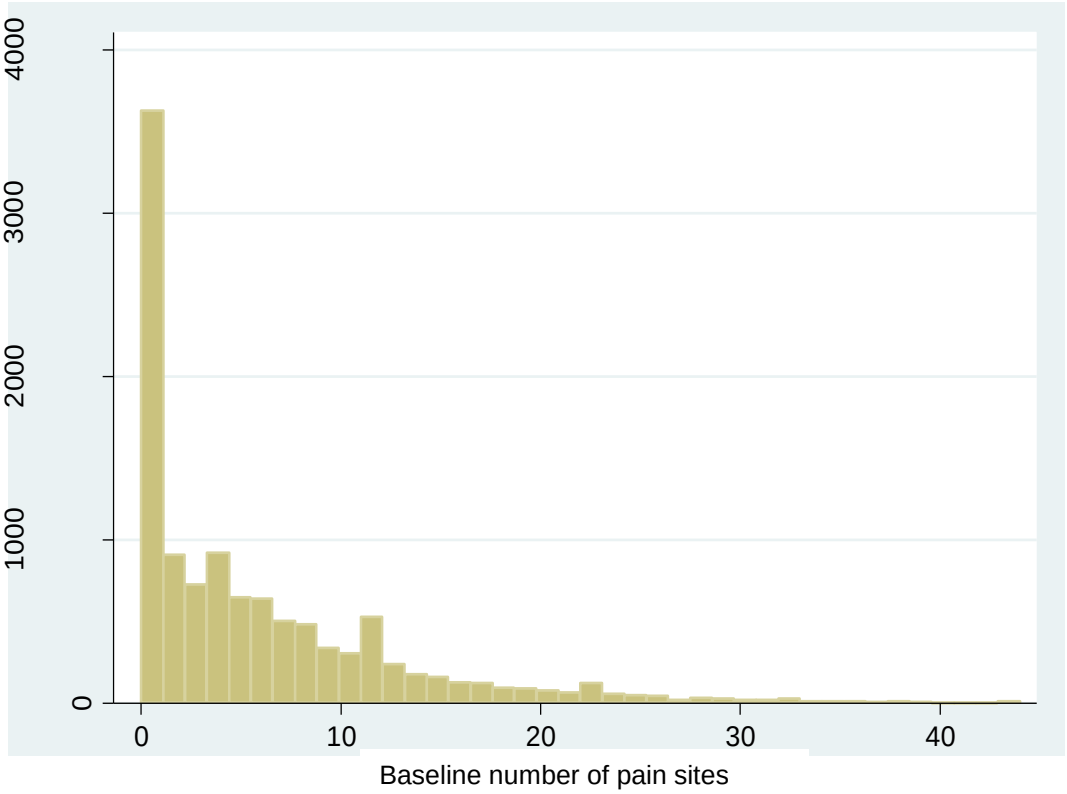
8.4.2 Pain and associations

8.4.2.1 Pain distributions

The prevalence of reported pain within thesis sample A and thesis sample B is 72.4% (n=8237) and 72.2% (n=3167) respectively. The number of pain sites is skewed towards 0, with 26.6% (3,026 respondents) of the sample reporting no pain in thesis sample A. In thesis sample A, 5.3% (605) of respondents reported single site pain, indicating that multisite pain was the most common presentation of pain within the sample. 8.0% (910) reported two sites of pain, 6.4% (728) reported 3 sites, 8.1% (921) reported 4 sites and then the frequencies reduced from 5.7% (652) reporting 5 pain sites to 7 people (0.06%) reporting 44 pain sites. Figure 8.1 presents the distribution of number of pain sites. Thesis sample B followed a very similar pattern of pain distribution and the difference between the mean number of pain sites between thesis samples A (mean number of pain sites 6.09 (95% CI 5.96-6.23) and B (mean number of pain sites 6.00 (95% CI 5.79-6.21)) was not statistically significant (p=0.56).

27.6% (3,138) of respondents reported no pain, 45.5% (5,175) reported some pain and 26.9% (3,062) met the criteria for ACR definition for widespread pain in thesis sample A; the corresponding figures for thesis sample B were 27.8% (1,219) reported no pain, 44.8% (1,965) reported some pain) and 27.4% (1,202) reported widespread pain. The differences in distribution of the widespread pain measure between thesis samples was not significant (p=0.47).

Figure 8.1 The distribution of the number of pain sites within thesis sample A (n=11,375)



8.4.2.2 Pain and demographic covariates

Table 8.7 outlines associations with the number of pain sites, pain widespreadness and demographic covariates. The mean number of pain sites is not statistically significantly associated with age when analysed as a continuous measure; age is statistically significantly associated with widespreadness although a difference in mean age of less than 12 months suggests that this difference is not clinically significant. Females are statistically significantly more likely to report more number of pain sites (mean number for women rounded to 7, compared with a mean for men of 5) and report more widespread pain.

Table 8.7 Cross-sectional associations between multisite pain and demographics in thesis sample A (n=11,375)

Variable	Number of pain sites Mean (95% CI)		No pain n=3138	Some pain n=5175	Widespread pain n=3062	P values
Age, years Mean (95% CI)	50-54	5.9 (5.5-6.2)	66.1 (65.7-66.4)	66.2 (65.9-66.5)	65.3 (65.9-66.4)	NPS & categorical age: chi squared p= 0.07 NPS & continuous age: Tau-b p of H_0 = 0.27 Widespread pain measure: p=0.01
	55-59	6.3 (6.0-6.6)				
	60-64	6.4 (6.0-6.7)				
	65-69	6.1 (5.8-6.4)				
	70-74	5.6 (5.3-6.0)				
	75-79	6.2 (5.8-6.6)				
	80-84	6.2 (5.7-6.7)				
	85-89	5.7 (5.0-6.5)				
	90-94	6.0 (4.6-7.4)				
	95-99	3.2 (0.8-5.5)				
Sex Male (n, %) Female (n, %)	5.4 (5.3-5.6) 6.7 (6.5-6.9)		1575 (29.9) 1563 (25.6)	2459 (46.7) 2716 (44.4)	1229 (23.3) 1833 (30.0)	NPS: Chi squared p< 0.01 Widespread pain: P<0.01
Education > 16y Yes No Missing	5.2 (4.8-5.5) 6.2 (6.1-6.4) 6.6 (5.6-7.4)		465 (33.7) 2623 (26.8) 50 (25.0)	613 (44.4) 4476 (45.7) 86 (43.0)	304 (22.0) 2694 (27.5) 64 (32.0)	NPS: Chi squared p <0.01 Widespreadness: P<0.01*
Occupational class Manual Non-manual Unknown	6.3 (6.1-6.5) 5.6 (5.4-5.8) 7.0 (6.5-7.6)		1669 (26.1) 1274 (30.7) 195 (23.4)	2881 (45.1) 1903 (45.8) 391 (47.0)	1839 (28.8) 977 (23.5) 246 (29.6)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
Income adequacy Adequate Inadequate Unknown	4.9 (4.8-5.1) 7.5 (7.3-3.8) 7.2 (6.1-8.3)		2022 (32.0) 1074 (22.1) 42 (21.3)	2941 (46.5) 2143 (44.1) 91 (46.2)	1357 (21.5) 1641 (33.8) 64 (32.5)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
IMD Least deprived 2nd least dep. Mid deprived 2nd most dep. Most deprived Missing	5.2 (4.9-5.4) 5.5 (5.2-5.8) 6.0 (5.7-6.3) 6.6 (6.3-6.9) 7.2 (6.9-7.6) 2.3 (-5.9-13.9)		700 (30.5) 704 (29.9) 618 (27.3) 587 (26.6) 528 (23.5) 1 (33.3)	1089 (47.5) 1078 (45.9) 1044 (46.1) 982 (44.4) 981 (43.6) 1 (33.3)	506 (22.1) 569 (24.2) 603 (26.6) 642 (29.0) 741 (32.9) 1 (33.3)	NPS: Chi squared p <0.01 Widespreadness: P<0.01

NPS = number of pain sites; P of H_0 = probability of null hypothesis being true; *this significance value tests for differences between groups, excluding the 'unknown' categories; IMD = Index of multiple deprivation; Education > 16y = continuing in full time education beyond aged 16 years; dep.=deprived

Full time education status is statistically significantly associated with both pain measures, with a lower number of pain sites and widespread pain reported amongst those continuing in full time education after leaving school. Occupational class is also statistically significantly associated with both pain measures; manual workers reported a greater number of pain sites than non-manual workers although when the number is rounded the mean number of 6 it is the same for both groups. Manual workers also reported more widespread pain than non-manual workers (28.8% (1839 respondents) compared with 23.5% (977 respondents). IMD is statistically significantly associated with the number of pain sites and the distribution of the widespread pain measure. The number of pain sites increases with rising levels of deprivation from 5.2 in the least deprived category to 7.2 in the most deprived category. The prevalence of widespread pain also increases with increasing deprivation, from 22.1% (506 respondents) in the least deprived area to 32.9% (741 respondents) in the most deprived area.

8.4.2.3 Pain and medical condition covariates

Multimorbidity was statistically significantly associated with pain, with a greater number of pain sites and prevalence of widespread pain reported amongst those with higher CCI scores; for example, the mean number of pain sites and percentage of respondents reporting widespread pain was 5.6 and 25.5% (2159 respondents) respectively for those with no Charlson-scored morbidities and 7.8 and 32% (322 respondents) respectively for those with CCI scores between 2 and 8 (table 8.8). Respondents with a BMI in the normal range had statistically significant lower mean number of pain sites and proportion of widespread pain compared to their underweight, overweight and obese counterparts, although the mean BMIs for each widespread category were all within the ‘overweight’ range

and the two-point difference in BMI (25.7kg/m^2 compared to 27.6kg/m^2) is not clinically significant. Respondents reporting dizziness, hearing impairment or visual impairment were all statistically significantly more likely to report a larger number of pain sites and more widespread pain. The most marked difference was seen in the dizziness grouping, where those reporting dizziness had 4 additional pain sites and 20% more reported widespread pain than their non-dizzy counterparts.

Table 8.8 Cross-sectional associations between multisite pain and physical health indicators in thesis sample A (n=11,375)

Variable	Number of pain sites Mean (95% CI)	No pain (%)	Some pain (%)	Widespread pain (%)	P values
Multimorbidity CCI 0 1 2	 5.6 (5.5-5.8) 7.2 (6.9-7.6) 7.8 (7.3-8.4)	 2461 (29.1) 443 (23.3) 234 (23.3)	 3851 (45.5) 875 (46.1) 449 (44.7)	 2159 (25.5) 581 (30.6) 322 (32.0)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
BMI n = 10959 Underweight Normal weight Overweight Obese Very obese Missing Continuous Mean range n	 6.5 (5.2-7.7) 5.1 (4.9-5.3) 6.1 (5.9-6.3) 7.8 (7.5-8.2) 11.3 (9.8-12.8) 6.4 (5.6-7.1) 	 25.7 14.4-60.2 3030	 26.7 13.8 – 70.3 4982	 27.6 11.9 – 71.5 2947	NPS & categorical BMI: Chi squared p <0.01 NPS & continuous BMI: Tau-b = 0.11 P of H_0 < 0.01 Widespreadness: p<0.01
Dizziness Yes No	 9.4 (9.1-5.1) 5.0 (4.9-5.2)	 466 (16.6) 2672 (31.2)	 1155 (41.1) 4020 (46.9)	 1188 (42.3) 1874 (21.9)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
Hearing problem Yes No	 7.3 (6.9-7.6) 5.8 (6.7-6.0)	 435 (20.7) 2703 (29.2)	 994 (47.3) 4181 (45.1)	 673 (32.0) 2389 (25.8)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
Vision problem Yes No	 7.8 (7.4-8.1) 5.7 (5.5-5.8)	 518 (22.0) 2620 (29.0)	 1036 (44.0) 4139 (45.9)	 805 (34.1) 2257 (25.0)	NPS: Chi squared p <0.01 Widespreadness: P<0.01
NPS= number of pain sites; CCI = Charlson comorbidity Index: 0 = no CCI morbidities, 1= 1 CCI morbidity, 2= 2-8 CCI morbidities; BMI = body mass index					

8.4.2.4 Pain and mental health covariates

The mean number of pain sites is statistically significantly associated with increasing scores on the anxiety symptom scoring scale, from a mean of 5 pain sites reported in those with minimal symptoms and 10 in those with likely clinical anxiety (table 8.9).

Table 8.9 Cross-sectional associations between multisite pain and mental health indicators in thesis sample A (n=11,375)

Variable	Number of pain sites Mean (95% CI)	No pain (%)	Some pain (%)	Widespread pain (%)	P values
Anxiety score 0-7 8-10 11+ Missing (n=265) n= 11110* Continuous Mean score SD n=11110	 4.6 (4.5-4.8) 7.4 (7.1-7.7) 9.8 (9.4-10.2) 6.4 (5.5-7.4) 	 5.2 (0-21) SD 3.8 n= 2077*	 6.6 (0-21) SD 4.0 n= 5043	 8.4 (0-21) SD 4.3 n= 2990	 NPS & categorical anxiety score: Chi squared p=<0.01 Widespreadness: p<0.01
Depression 0-7 8-10 11+ Missing n=11120 Continuous Mean score SD n=11110	 5.0 (4.9-5.2) 9.1 (8.7-9.5) 11.4 (10.8-12.0) 6.2 (5.3-7.2) 3.4 (0-21) SD 3.2 n= 3078	 4.7 (0-21) SD = 3.5 n= 5049	 6.3 (0-21) SD = 3.9 n= 2993	 NPS & categorical depression score: Chi squared p=<0.01 Widespreadness: p<0.01
Cognitive complaint No Mild Moderate Severe Missing n=10774* Continuous Mean (range) SD n=10774	 4.3 (4.2-4.5) 6.9 (6.6-7.3) 7.9 (7.5-8.2) 9.9 (9.4-10.4) 7.1 (6.4-7.7) 8.6 (0-100) SD 18.2 n=3018	 14.0 (0-100) SD 22.5 n=4897	 22.3 (0-100) SD 27.4 n=2859	 NPS & categorical cognitive complaint score: Chi squared p=<0.01 Widespreadness: p<0.01
n=xxxxx* = number of non-missing values in each variable; anxiety and depression scale scores: 0-7 = normal, 8-10 = borderline, 11 or over = clinical 'caseness'; NPS= number of pain sites					

The same pattern was seen in depression, where the mean number of pain sites increased from 5 in those with minimal symptoms to 11 in those with likely clinical depression. This pattern is reflected in the widespreadness measure; widespread pain was reported in one fifth of respondents with low anxiety or depression scores and in almost half of those with high anxiety and depression scores. Cognitive complaint followed a similar trend, with lower scores statistically significantly less likely to report multisite pain and widespread pain.

8.4.2.5 Pain and medication

Table 8.10 shows that stronger analgesics statistically significantly associated with a greater number of pain sites and more widespread pain (table 8.10).

Table 8.10 Cross-sectional associations between multisite pain and medication measures in thesis sample A (n=11,375)

Variable	Number of pain sites Mean (95% CI)	No pain (%)	Some pain (%)	Widespread pain (%)	P values
Total medication					NPS & categorical total medication: Chi squared p=<0.01 Widespreadness: p<0.01
0 meds	3.8 (3.6-3.9)				
1-2 meds	5.0 (4.8-5.2)				
3-4 meds	6.0 (6.8-6.4)				
5-7 meds	7.8 (7.5-8.1)				
8+meds	9.9 (9.4-10.3)				
Continuous					
Mean		2.5 (2.4-2.6)	3.4 (3.4-3.6)	4.6 (4.5-4.8)	
SD		2.8	3.4	3.9	
n		3,138	5,175	3,062	
Pain medication					NPS: Chi squared p=<0.01 Widespreadness: p<0.01
0	4.6 (4.5-4.8)	2838 (34.5)	3696 (44.9)	1697 (20.6)	
1	7.0 (6.5-7.5)	163 (18.8)	433 (49.9)	271 (31.3)	
2	10.2 (9.6-10.9)	55 (7.1)	376 (48.7)	341 (44.2)	
3	10.6 (10.0-11.2)	53 (6.8)	433 (45.9)	369 (47.3)	
4	12.2 (11.5-12.9)	29 (4.0)	312 (43.0)	384 (53.0)	
NSAID use					NPS: Chi squared p=<0.01 Widespreadness: p<0.01
Yes	10.3 (9.8-10.8)	75 (6.1)	596 (48.3)	562 (45.6)	
No	5.6 (5.5-5.7)	3063 (30.2)	4579 (45.2)	2500 (24.7)	

NPS= number of pain sites; Pain medication maximum category: 0 No analgesics, 1 Basic analgesics, 2 Weak combination opioids, 3 Moderate combination opioids and opioids , 4 Strong combination opioids and opioids, 5 Very strong single opioids; SD = standard deviation; NSAID = non-steroidal anti-inflammatory drugs

The total medication number increases with the number of pain sites, from a mean of 4 pain sites reported by those with no prescribed medication and those with 8 or more medications reporting a mean of 10 pain sites. From all those taking 8 or more medications, almost three times the number of respondents have widespread pain than no pain. The mean number of pain sites increases with increasing analgesic strength and this is statistically significant. Fewer NSAIDs are prescribed in the widespread group than the 'some pain' group.

8.4.2.6 Pain and physical functioning

Declining physical functioning, as measured by difficulty walking, is statistically significantly associated with increasing number of pain sites (table 8.11). Respondents reporting a lot of difficulty had a mean number of pain sites of 12, compared to those reporting no difficulty with a mean of 4. Almost 50% (655 respondents) of those with a lot of difficulty reported widespread pain, twice the number of those who reported widespread pain with no physical functioning problems (19.9% (1572 respondents).

Table 8.11 Cross-sectional associations between multisite pain and physical functioning in thesis sample A (n=11,375)

Variable	Number of pain sites Mean (95% CI)	No pain (%)	Some pain (%)	Widespread pain (%)	p values
Physical functioning (difficulty walking 100 yards)					NPS: Chi p<0.01
Yes, a lot	11.7 (11.3-12.3)	130 (9.4)	593 (43.0)	655 (47.5)	
Yes, a little	9.2 (8.6-9.6)	236 (12.6)	850 (45.3)	790 (42.1)	Widespreadness: p<0.01
No	4.4 (4.3-4.5)	2714 (34.3)	3682 (45.9)	1572 (19.9)	
Missing (n=203) n=11172	5.2 (4.2-6.1)	58 (28.6)	100 (49.3)	45 (22.2)	
significance value tests for differences between groups, excluding the 'unknown' category					

8.4.2.7 Pain and covariate associations: summary

This section has found that the only covariate not statistically significantly associated with pain was age. Women reported a greater number of pain sites and more widespread pain than men. Indicators of lower socioeconomic position were associated with more pain sites and more widespreadness of pain. Those reporting higher numbers of pain sites had more comorbidities, poorer mental health indicator scores, were taking more medication and had worse physical functioning than those reporting lower number of pain sites.

8.5 Discussion

8.5.1 Summary of findings

This chapter has described the distribution of pain and covariates in thesis samples A (n=11,375: baseline NorStOP respondents who consented to medical record review and who gave consistent answers to the pain questions) and B (n=4386: respondents from thesis sample A who completed all NorStOP survey follow up and provided consistent answers to the pain question). The prevalence of pain, the mean number of pain sites and the distribution of the widespread pain measure are very similar in both samples. With the exceptions of NSAID use, anxiety scores, BMI and sex, all other covariates are distributed statistically significantly differently between thesis samples A and B. These differences mean thesis sample B has lower proportions of multimorbidity, dizziness, visual disturbance and hearing impairment, lower scores on depression and cognitive complaint measures, fewer prescribed medications and fewer strong analgesics, and less difficulties with physical functioning than thesis sample A. These

differences are likely to be due to the healthy cohort effect, where survivors who remain in the cohort study generally do so because they are fitter and in better overall health.

All covariates are statistically significantly associated with pain status except age and must therefore all be considered at possible influencers of the relationship between pain and falls.

8.5.2 How findings fit with current literature and what is new

The prevalence of multisite pain in thesis sample A (73.4%) is higher than comparable point prevalence rates taken over a 4-week period, for example Scudds et al (2001) who reported a prevalence of 55% in adults aged over 70 years old. This could be explained by the construction process of thesis sample A, in which NorStOP respondents who did not complete the pain questions consistently (see Chapter 7) were excluded. Thus, it may be that those who did not have pain did not feel the need to complete the pain questions and were excluded. Excluding a greater proportion of those with no pain would lead to a higher prevalence of pain within thesis sample A.

The prevalence of widespread pain in thesis sample A was 26.9%, a higher prevalence than other studies have found. For example Docking et al (2015) found that the prevalence of chronic widespread pain (defining using the ACR definition provided in Chapter 2) was 21.0% in adults aged 55 years and older residing in rural communities, higher than the 17% for those living in urban communities (Docking et al, 2015). The prevalence estimate in thesis sample A might be due to the measure of pain in the last month rather than pain lasting for

at least 3 months in accordance with the ACR definition of widespread pain. The relatively high prevalence of widespread pain within thesis sample A may also be reflective of the local population who have preponderance for lower socioeconomic position, a status which has been shown to increase the risk of developing widespread pain (Davies et al, 2009).

Multisite pain was more common than single site pain in the thesis samples; this is an excepted finding as it is now well documented that single site pain is less likely than multisite pain, for example by Picavet and Schouten (2003).

Finding that age is not statistically significantly associated with pain is expected, since evidence suggests that multisite pain is established as early as childhood and its course is unlikely to change over time (Papageorgiou et al, 2002). Nevertheless this is an interesting finding that has yet to be satisfactorily explained within the literature. Perhaps this is due to older people's normalisation of the pain experience and their belief that it is not treatable or curable.

The magnitude of anxiety and depression symptoms and the impact on number of pain sites is important; a score suggestive of diagnosable anxiety or depression in respondents in thesis sample A doubled the number of pain sites reported compared to pain-free counterparts. It is well known that anxiety and depression are associated with pain, for example Nicholl et al. (2014) who reported that those with multisite pain are more likely to have depressive disorders and Heer et al. (2014) who found the presence of anxiety was statistically significantly associated with a higher pain scores. The strength of this association in thesis sample A suggests that particular attention is paid to these factors during analysis to ensure that any risk of falls associated with pain has taken account of mood disturbance.

Another key finding is the statistically significant association of pain with dizziness, hearing and vision, especially since pain reporting does not significantly increase with advancing age. Associations between these covariates and pain are not widely reported in the literature and it is important that this link is explored further outside this thesis. Perhaps it is the side effects of medications prescribed for pain that is responsible for this association, for example, amitriptyline is often trialled for widespread pain and dizziness is a possible side effect of this medication. Perhaps the pain precludes exercise due to the associated limitation in physical functioning, as demonstrated by Mottram et al (2008). In turn, this reduced exercise reduces general health, contributes to increasing comorbidities (as demonstrated in this analysis, that pain is associated with higher multimorbidity scores) and therefore dizziness is a consequence of physical health problems and side effects of medication used to manage multimorbidity. This cross-sectional analysis can only measure associations between variables, it cannot suggest causality and so it is not possible to conclude that the poor vision, poor hearing and dizziness are contributing to the pain, or vice versa. However these variables are linked, it is likely to be a complex pathway with many additional influencing factors and this certainly warrants further explanation, particularly in the context of general practice. Would reducing hearing deficits by ensuring older people have access to hearing assessments and aids, or reducing visual disturbances by ensuring timely access to phacoemulsification (cataract surgery), screening for type II diabetes mellitus or advising particular diets to help reduce the burden of wet macular degeneration, or more aggressive investigation and management of dizziness result in lowering the prevalence of multisite pain?

8.5.3 Strengths

This chapter has been able to test the direction and strength of association between pain and a wide variety of covariates that may also be associated, or are known to be associated, with an increased risk of falls. Testing the associations of these variables with pain means a better understanding of their possible influence on the relationship between pain and falls in this thesis. Covariates can now be accounted for during analyses to minimise the risk of bias due to confounding, or misinterpretation of results that may, in part, be contributed to by other covariates.

Thesis sample A is a large study sample containing 11,375 older adults; as such these univariate associations are more likely to be close to the true effect estimate than would be seen in a smaller sample.

This chapter has measured the impact of study attrition on the distribution of covariates in thesis sample B when compared to sample A. Knowledge of this difference in samples enables the risk of bias due to study attrition to be minimised sufficiently.

The pain measures used in this chapter, and thesis, are widely used and were derived by a validated tool using a body manikin (Lacey et al, 2014). Furthermore, misclassification bias is reduced as respondents who completed the pain screening question and body manikin inconsistently were excluded from analysis; the pain measure is therefore designed and used in a way that sufficiently limits bias from this source.

8.5.4 Limitations

The main limitation of this chapter is the exclusive restriction to univariate analysis. Whilst this serves the purpose of establishing which covariates are likely to impact the relationship between pain and falls due to their statistically significant relationship with pain, it does not explore those individual associations in a real life clinical context. For example, it may be that one of the statistically significant associations with pain disappears when a second variable is added to the equation.

All measured associations between pain and covariates are cross-sectional as the information is taken at the same time point. It is therefore not possible to establish causality or temporality. For the purpose of this thesis, a cross-sectional association is satisfactory evidence of an association that is statistically significant and must be accounted for when analysing the relationship between pain and falls. Future studies measuring any pain-falls relationship may find it useful to assess changes in covariates according to pain status over time as this may be useful in further reducing the risk of falls in older people. For example, if hearing and visual impairments are managed proactively, does this reduce the overall burden of pain and thus might reduce the risk of falls? Mundal et al (2016) undertook a study designed to explore the change in the number of pain sites and associations over an 11 year period in 78,973 adults aged 20 years and older in Norway; 26,875 individuals completed all follow ups and had complete information about pain status. The study found that, within the 78,973 population, the mean number of pain sites didn't change over the 11 year period. Within-subject analyses however found that a change in number of pain sites was not dependent on pain extent at baseline; anxiety and depression symptoms, sleeping problems and a high BMI

were found to be the strongest predictors of an increase in pain sites recorded over time (Mundal et al, 2016). This is significant for this thesis; if a temporal relationship between pain and covariates can be established, then control of these covariates from baseline (for example, identifying and treating depression at an early stage) may reduce future pain levels and therefore reduce the risk of future falls. This thesis is not designed to answer this question, although moving forward this would be an interesting point to explore further with a clear potential role for primary care health professionals.

8.5.5 Informing the thesis

All covariates, except age, are significantly associated with pain in thesis sample A. A case can therefore be made to include all of these covariates in analyses measuring the risk of falls due to pain, regardless of whether each covariate is associated with falls in univariate analysis. Undertaking statistical testing of interactions goes some way towards formally measuring such complex relationships between these covariates and this is explained further and undertaken during analyses in Chapters 10 and 11. Given the association of pain and all covariates except age, the exclusion of any covariate on the basis of a non-statistically significant association with falls in univariate analysis (conducted in chapter 9) may lead to an analysis that is not reflective of real life daily clinical practice, where patients present with multisite pain, display some depressive symptoms, have trouble with their memory and are on multiple medications.

8.5.6 Chapter summary

This chapter has described the distribution of pain across thesis sample A and B and put this into context with existing literature. Covariate distributions in thesis samples A and B have been presented and shown to be statistically significant

different with thesis sample B containing respondents with fewer comorbidities, better mental health measures, fewer medication and strong analgesic prescriptions and less physical functioning limitation. Univariate associations between pain and covariates have found that all but age are statistically significantly associated and the majority of these associations are to be expected based on the current literature. Associations with hearing, vision and dizziness are new findings which warrant further exploration in future studies, along with further study of change in covariates and pain status over time and the role that this may have in falls prevention. The next chapter examines the prevalence of falls within the study samples and explores univariate associations between covariates and falls.

Chapter 9: falls prevalence and univariate analyses of putative falls predictors

9.1 Overview

This chapter describes the prevalence of self-reported, GP-recorded and HES-recorded falls in thesis sample A (n=11,375). Univariate associations with self-reported are then explored and placed within the context of the current literature.

9.2 Rationale and chapter objectives

Chapter 8 concluded that all covariates must be included in an analysis that explores the relationship between pain and falls. To undertake a clinically useful examination of the pain and falls relationship it is first necessary to describe the prevalence of falls within the thesis' study sample to appreciate the size of the problem in clinical practice. It is also essential to understand any association between covariates and falls in univariate analysis to then begin to interpret the possible impacts of each covariate on the pain-falls relationship. Therefore, this chapter seeks to:

i) Describe the prevalence of self-reported, GP-recorded and HES-recorded falls in thesis sample A (the sample containing baseline NorStOP respondents who consented to medical record review and completed pain questions consistently);

ii) To undertake univariate analyses of pain and each covariate and their relationship with future self-reported falls.

9.3 Methods

9.3.1 Study sample, pain, covariates and fall measures

Thesis sample A will be used to measure prevalence since its larger size means it is more likely to be powered sufficiently to detect a difference between groups. Thesis sample B will be used to explore univariate relationships with future self-reported falls since this sample has complete follow up; thesis sample A would have a large number of missing data for three and six year self-reported falls due to loss to follow up at three and six years.

Pain and covariates are measured as described in Chapter 6 and information on covariates is taken from the baseline NorSTOP survey.

The prevalence of GP-recorded and HES-recorded falls will be examined using two outcomes i) the number of respondents who have a GP-recorded or HES-recorded fall in their records (i.e. 'ever fallen'); and ii) the total number of GP-recorded or HES-recorded falls for each respondent.

9.3.2 Falls prevalence time frames

For self-reported falls, period prevalence is estimated over the three months prior to survey return. Thus, there is a gap of 2 years and 9 months during which respondents may fall but that fall would not be recorded here. The implications of the gap in the self-reporting period are explored in this chapter's discussion.

For falls recorded in GP consultation records and HES data, the period prevalence is estimated from the start of the respondent's corresponding NorStOP baseline survey mail out until the end of NorStOP3 six year follow up for respondents who completed all follow up surveys. For respondents who did not complete three year

follow up, their study period ends at the end of the corresponding three year survey mailout period. Therefore, respondents in NorStOP1 who complete follow up surveys will have data over ten years, those in NorStOP3 who complete all follow up surveys will have data over six years and those in any of the NorStOP cohorts who do not complete three year follow up will have their data collected over three years. The implications of these differences are explored in this chapter's discussion. The number of respondents who have a GP or HES recorded fall within this time frame will be used as the 'faller' group in univariate and cross-sectional analyses.

9.3.3 Statistical testing

9.3.3.1 Prevalence of falls

Simple frequencies are used to describe the prevalence of self-reported, GP-recorded and HES-recorded falls within thesis sample A. The number of individuals who fall and the number of falls that each individual sustains is calculated.

9.3.3.2 Univariate associations with falls

9.3.3.2.1 Logistic regression theory

Logistic regression is used to measure the univariate association between each covariate and future self-reported falls within thesis sample B. Logistic regression is now a standard method of analysis when describing the relationship between a binary response variable (falls) and one or more explanatory variables (for

example pain, anxiety, depression and other covariates) (Hosmer & Lemeshow, 2000).

The basic premise of logistic regression is a 'logit transformed' formula

$$g(x)=\beta_0 + \beta_1 x$$

where *g(x)* is the log of the conditional mean of *Y* given *x* when the logistic distribution is used (Hosmer & Lemeshow, 2000), for example, the conditional outcome of falls as predicted by the presence of pain. Logistic regression becomes clinically useful when multiple outcome predictors are considered, which is discussed further in Chapter 10.

9.3.3.2.2 Interpretation of logistic regression model output

Logistic regression is interpreted using odds ratios. An odds ratio is a measure of association that looks at how much more likely the outcome is in the exposed group compared to the unexposed group, for example how much more likely respondents with pain are to fall than respondents with no pain. In this thesis' analyses, an odds of 1 means that there is no difference between groups with pain or no pain, or between different numbers of pain sites; an odds ratio <1 means that the odds of falling with pain (or a greater number of pain sites) are less than those without pain (or a lower number of pain sites); an odds ratio of >1 means that the odds of falling in those with pain (or a greater number of pain sites) is higher than those with no pain (or a lower number of pain sites).

9.4 Results: Prevalence of falls

9.4.1 Self-reported falls

12.5% (1,417) of thesis sample A reported a fall in the baseline NorStOP survey; falls prevalence in the three months prior to baseline survey is therefore 12.5%.

14.4% (1,056) of respondents reported a fall in the three months prior to the 3 year follow up survey and 14.2% (685) reported a fall in the three months prior to 6 year follow up.

9.4.2 GP-recorded falls

783 respondents had one or more GP-recorded fall, giving a period prevalence of 6.9%. 508 respondents (4.5%) had one fall and 275 (2.4%) had more than one fall. Table 9.1 presents the number of falls for each respondent. Two respondents had 20 or more fall-related codes in their records throughout the study period.

Table 9.1 The frequency of GP-recorded falls within thesis sample A (n=11,375).

Number of GP-recorded falls per respondent	Frequency (%)
0	10,592 (93.1)
1	508 (4.5)
2	143 (1.3)
3	61(0.7)
4	32 (0.4)
5	9 (<0.1)
6	12 (0.1)
7	4 (<0.1)
8	6 (<0.1)
9	3 (<0.1)
11	1 (<0.1)
12	2 (<0.1)
20	1 (<0.1)
23	1 (<0.1)

9.4.3 HES recorded falls

804 respondents had one or more HES-recorded fall, giving a period prevalence of 7.1%. 648 respondents had one HES-recorded fall (5.7%) and 156 respondents (1.4%) had more than one HES-recorded fall. Two respondents had 8 HES-recorded falls; two of these fall dates were clustered within 48 hours and other dates were spread across the study period.

Table 9.2 The frequency of HEs-recorded falls in thesis sample A (11,375)

Number of HES recorded falls per respondent	Frequency (%)
0	10,571 (92.9)
1	648 (5.7)
2	103 (0.9)
3	33 (0.3)
4	14 (0.1)
6	3 (<0.1)
7	1 (<0.1)
8	1 (<0.1)

9.4.4 Fall-related injuries recorded in HES

To assess the reliability of coding falls within the HES dataset, the prevalence of fall-related injuries is measured. 738 respondents (6.5%) were admitted to hospital with fall-related injuries during the equivalent time period, fewer than the number of respondents admitted with a HES fall-related code.

9.4.5 Summary

Self-reported falls were the most prevalent amongst respondents in thesis sample A (12.5%). The prevalence of HES-recorded falls was higher than GP-recorded falls (7.1% and 6.9% respectively). These results will be explored further in the Discussion section of this chapter.

9.5 Results: Univariate associations with future self-reported falls

A summary of the univariate associations between baseline pain and covariates and future self-reported falls at three and six years is provided in table 9.3. Increasing age, higher deprivation levels, a higher BMI, the presence of dizziness, hearing difficulty and vision impairment, 2 or more CCI comorbidities, increasing anxiety, increasing depression and increasing cognitive complaint scores, increasing total medication count, all categories of analgesics (except very strong opioids, likely due to small numbers) , NSAID use, limitation in physical functioning and baseline self-reported fall were all associated with a statistically significant increased risk of future three, or six, year self-reported fall.

The biggest predictors of future self-reported falls are baseline reported fall, where the odds of falling at three years are 4.64 greater than those with no baseline fall, and 3.67 greater for a fall at six years. A 'lot' of limitation in physical functioning conferred odds of 3.89 for three year fall and 4.42 for six year fall compared to those with no limitation in physical functioning. Respondents who reported dizziness had more than double the odds of falling at three and six years than their non-dizzy counterparts.

Being male and reporting adequate income were associated with a statistically significant reduced risk of future three, or six, year reported fall; being male reduced the odds of falling at three and six years by approximately 30%.

Not continuing in full time education and manual occupations are statistically significantly associated with three year fall but not six year future fall.

Table 9.3 Self-reported falls and univariate associations with multisite pain and covariates in a sample of complete cohort follow up

Covariate (OR, 95% CI)	3 year self-reported fall	6 year self-reported fall
Age	**1.02 (1.01-1.03)**	**1.04 (1.03-1.05)**
Sex		
Female	Referent	Referent
Male	**0.67 (0.56-0.80)**	**0.68 (0.57-0.81)**
Full time education >16y (n=4319)		
Yes	Referent	Referent
No	1.28 (0.99-1.67)	0.98 (0.77-1.23)
Occupational Class (n=4176)		
Manual	Referent	Referent
Non-manual	**0.67 (0.56-0.81)**	0.86 (0.72-1.03)
Income adequacy (n=4333)		
Inadequate	Referent	Referent
Adequate	**0.61 (0.51-0.73)**	**0.57 (0.48-0.67)**
IMD (n=4385)		
Least deprived	Referent	Referent
2nd least deprived	0.99 (0.75-1.31)	1.28 (0.98-1.68)
Mid-deprived	1.15 (0.87-1.53)	**1.32 (1.00-1.74)**
2nd most deprived	**1.40 (1.06-1.85)**	1.28 (0.96-1.69)
Most deprived	**1.59 (1.20-2.10)**	**1.85 (1.41-2.43)**
BMI (n=4281)	**1.04 (1.03-1.06)**	**1.03 (1.02-1.05)**
Dizziness	**2.36 (1.94-2.85)**	**2.83 (2.36-3.40)**
Hearing difficulty	1.18 (0.93-1.50)	**1.33 (1.06-1.67)**
Visual disturbance	**1.58 (1.27-1.97)**	**1.78 (1.44-2.19)**
Comorbidities (CCI)		
0	Referent	Referent
1	1.21 (0.95-1.55)	1.22 (0.96-1.55)
2-8	1.18 (0.81-1.69)	**1.74 (1.27-2.39)**
Anxiety score (n=4311)	**1.11 (1.09-1.13)**	**1.07 (1.05-1.10)**
Depression score(n=4311)	**1.14(1.12-1.17)**	**1.13 (1.10-1.15)**
Cognitive complaint (n=4232)	**1.03 (1.02-1.03)**	**1.02 (1.02-1.02)**
Total medication number	**1.14 (1.11-1.17)**	**1.13 (1.11-1.16)**
Maximum analgesic category		
No medication	Referent	Referent
Basic analgesics	**1.75 (1.24-2.47)**	**1.58(1.13-2.21)**
Weak opioids	**2.29 (1.62-3.24)**	**2.36(1.70-3.29)**
Moderate opioids	**2.44 (1.79-3.34)**	**2.15 (1.57-2.92)**
Strong opioids	**3.58 (2.64-4.86)**	**3.14 (2.32-4.26)**
Very strong opioids	5.70 (0.95-34.2)	1.88 (0.21-16.8)
NSAID use		
No	Referent	Referent
Yes	**1.47 (1.14-1.90)**	**1.76 (1.38-2.23)**
Physical functioning (n=4342)		
No limitation	Referent	Referent
A little limitation	**2.31(1.84-2.91)**	**2.81 (2.26-3.49)**
A lot of limitation	**3.89 (2.95-5.12)**	**4.42 (3.39-5.78)**
Baseline self-reported fall	**4.64 (3.68-5.83)**	**3.67 (2.92-4.63)**

n = 4386 unless otherwise stated; OR = odds ratio; 95% CI= 95% confidence interval; p = p value; **p<0.05 highlighted in bold;** Full time education >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation; BMI = body mass index; Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities;NSAID = non steroidal anti=inflammatory.

9.5.1 Summary: univariate associations with self-reported falls

Advancing age and being female are statistically significantly associated with recording of future self-reported falls. Manual work is statistically significantly associated with future self-reported falls and continuing in full time education is not statistically significantly associated with future self-reported falls. Income inadequacy and increased levels of deprivation are statistically significantly associated with future self-reported falls.

Multimorbidity, dizziness, vision and hearing impairment, total medication count and analgesic use (excepting NSAIDs) are statistically significantly associated with future self-reported falls. Anxiety, depression and cognitive complaint scores are statistically significantly associated with future self-reported falls and the difference in cognitive scores in particular is clinically meaningful. Physical functioning is statistically significantly associated with future self-reported falls.

9.6 Discussion

9.6.1 Summary of findings

The prevalence of falls within thesis sample A (n=11,375) is 12.5% for self-reported falls, 6.9% for GP-recorded falls and 7.1% for HES-recorded falls. Univariate analysis found that increasing age, being female, increasing mulitmorbidity, the presence of dizziness, vision or hearing impairment, an increase in all mental health measures, an increasing total medication count, stronger analgesics and worsening physical functioning are statistically significantly associated with an increased risk of future self-reported fall.

9.6.2 How findings fit in the current literature and what is new

Compared to previous research exploring self-reported falls, the falls prevalence reported in this thesis is low. For example, a recent UK-based study found that 28.4% of community dwelling adults aged 60 years and over had fallen in the past two years (Gale et al, 2016), with women falling more than men (29.1% and 23.5% respectively). The higher prevalence may be explained by the older cohort and the two year recall period. The extended recall period meant that respondents had more time in which to risk falling and therefore report higher falls prevalence than the thesis' sample in which respondents only considered a three month period; indeed, the difference in recall period is a recognised contributor to the variation in number of falls reported across the literature (Hauer et al, 2006).

The prevalence of GP-recorded falls is lower in the thesis than current published evidence, although no direct comparisons are available which is perhaps due to the challenges of coding of falls in GP records, a problem widely recognised by the GPs consulted over falls coding practices in this study. Gribbin et al (2009) analysed the incidence and mortality of falls amongst older people in primary care using The Health Improvement Network primary care database (THIN). The authors found 79,295 recorded fall-events over three years in 61,248 individuals, giving a falls rate of 3.58 (3.56-3.61 95% CI) recorded falls per 100 person years (Gribbin et al, 2009). Summing the number of GP falls reported in table 9.1 gives a total number of GP falls in thesis sample A of 1,403 falls in 11,375 respondents. Using a very approximate calculation to obtain an extrapolated estimate of falls prevalence in thesis sample A (these numbers or not comparable as the GP falls prevalence is taken over at least a three year period in this thesis), extrapolation of this thesis' sample to a similar size study as Gribbin's et al (2009), one might

expect to find approximately 20,000 falls. The difference between this approximate extrapolation figure of 20,000 and the recording of 79,295 fall events in Gribbin et al's (2009) study indicates that falls are likely to be under-coded in the GP records used in this thesis and the resulting prevalence is therefore likely to underestimate the true number of falls presenting to general practice.

There are no direct comparison of HES-recorded falls prevalence in published research. The closest comparison and most robust study is from The King's Fund who following the Torbay cohort, identified fallers requiring hospital admission from hospital and GP data and analysed associated health and social care costs (Tian et al, 2013). They found just over 1% of the Torbay population (adults aged 65 years old living in the community) had fallen between July and December 2010 (Tian et al, 2013). If this is extrapolated to represent my study time period (notwithstanding the impact of poor weather and icy conditions during the winter months and other external factors that would impact on the likelihood of falling), this would give an expected HEs-recorded falls prevalence in thesis sample A of approximately 24%, a considerably lower estimate than the presented prevalence of 7.1%). In order to check the reliability of falls-coding in HES in the event that evidence might suggest under-recording of HES falls, information was collected on fall-related injuries. The number of fall-related injuries is less than the number of fallers identified, thus indicating that falls likely to be coded relatively reliably in HES-APC data. The difference in fall rates between the two studies may be due to the inclusion of all fall-related ICD-10 codes including those related to occupational causes of fall which were excluded from this thesis' fall coding (as described in Chapter 6) or due to the older population of Torbay. It cannot be due

to a misclassification bias between the two studies since the same datasets were used.

Logic suggests that more respondents saw their GP about a few than ended up with a hospital admission relating to a fall, however the prevalence of GP-recorded falls is lower than HES-recorded falls within thesis sample A. The reasons for this are not clear. The most likely cause of this is under-coding of falls by GPs. This risks introducing misclassification bias where respondents who did attend their GP with a fall-related problem but were not coded as such were classified as a non-GP-recorded faller. This in turn may lead to an underestimation of associations with falls.

The majority of associations between covariates and falls reflect the literature covered in the review of falls risk factors detailed in Chapter 4. Unexpected associations are now highlighted, reasons for these associations are hypothesised and suggestions for future study are made.

Hearing impairment has been demonstrated to be a risk factor for self-reported falls. Assessment of hearing does not form part of the multifactorial risk assessment for falls prevention in older people advised by NICE (2013). The systematic review of hearing loss and falls by Jaim et al (2016) discussed in Chapter 4 also found an association, although the studies from which effect estimates were pooled were primarily cross-sectional. Jaim et al (2016) present biologically plausible explanations for this association, including co-existent vestibular dysfunction and resulting imbalance, and it will be interesting to explore whether this relationship exists during multivariable analysis.

Increasing anxiety and depression scores were found to be statistically significantly associated with future self-reported falls; these covariates do not currently feature in fall prevention guidelines (for example NICE, 2013). These findings reflect the literature, for example Hoffman et al (2017) who found that reporting depressive symptoms was a statistically significant risk factor for future falls risk, although this result was attenuated during multivariate analysis. It is imperative to assess the influence of depression upon future falls risk in multivariate analysis during subsequent thesis analyses since this may provide further evidence that depression is association with an increased risk of falls in older people and requires intervention to reduce falls risk. Anxiety has recently been association with an increased risk of future falls (Holloway et al, 2016) and it is important that further multivariate analyses are conducted to examine the ongoing relationship between anxiety and falls when other potentially influencing factors are accounted for.

Pain medication strength is statistically significantly associated with future self-reported falls. The relationship between pain medication strength and falls is also interesting as the group using moderate strength medications are less likely to self-report a fall than those using weak pain medications or strong pain medications. Perhaps this is due to better pain control that therefore reduces the risk of falls i.e. the risk of using opiate medication is negated by the overall reduction in pain and thus reduced risk of falls. This finding warrants further exploration as an extension to the thesis.

9.6.3 Strengths

As discussed in Chapter 8, one strength of this analysis is the relatively large sample size, larger than those studies included in the systematic review. Known falls risk factors have had their associations confirmed within thesis sample B, thus demonstrating that this sample is not an anomalous group that may not be comparable to the general population.

The use of three different fall measures enables a wider perspective of falls prevalence to be obtained; using only self-reported falls would not capture the burden of falls resulting in hospital admission, and using only hospital admission data would mean many respondents would be misclassified as 'non-fallers'.

Systematically measuring the association between each covariate and self-reported falls has provided a good understanding of the potential role of each covariate in future multivariable analyses.

9.6.4 Limitations

The reported prevalence of self-reported, GP-recorded and HES-recorded falls are not comparable due to the different time frames over which data were collected, thus conclusions about relative prevalence cannot be drawn. However, given that the self-reported falls are gathered over a three month period and GP and HES-recorded falls are gathered over a minimum three year period, it is reasonable to state that self-reported falls were the most prevalent type of fall in this study.

GP-recorded and HES-recorded falls identified respondents who have fallen multiple times. For example, one respondent was found to have 23 GP-recorded falls and two respondents had 8 HES-recorded falls. Steps were taken to reduce likelihood of the same fall event being counted multiple times by coding all falls

recorded on the same date as one fall. It is possible that multiple falls recorded over a 24 or 48 hour period may be reflect new falls, particularly in HES-APC data where sustaining a fall whilst an inpatient is not an unusual clinical scenario, thus fall-related codes that were more than 24 hours apart were counted as additional falls. Further inspection of the records of the respondent who had 23 GP-recorded falls found some of the fall dates were clustered together over a two week period. Multiple appointments in close succession could include frequent dressings of a fall-related injury or frequent follow up for new medications started (or stopped) since falling. Whatever the reason for GP attendance, it is clear that falls generate multiple appointments and add to the GP workload.

The self-report of falls relies on respondent recall and is therefore susceptible to recall bias, as found by Hannan et al (2010) who compared telephone recall with daily falls calendar completion and found that older people failed to recall 25% of falls they had documented on their calendar in the three months prior to the telephone call. Self-reported fall prevalence in this thesis may therefore be an underestimate of the true picture due to recall bias.

As discussed above, the low prevalence of GP-recorded falls suggests that thesis sample A may be susceptible to misclassification bias, whereby respondents are wrongly coded as 'non-fallers' simply because the GP has not coded the consultation using a fall-related READ code, this might lead to an underestimation of the true association between pain and GP-recorded falls.

Taking a wider view of the use of HES-APC data to capture falls requiring hospital admission, it is suspected that HES-APC data might be susceptible to under-

recording of falls since often the patient presents with the consequence of the fall and this is what is recorded.

9.6.5 Informing the thesis

The identification of a relatively low prevalence of self-reported, GP-recorded and HES-recorded falls may lead to an underestimation of the magnitude of the relationship between pain and falls. This potential problem has been highlighted and future analyses can now be interpreted within this context. Almost all of the covariates tested have been found to be statistically significantly associated with future self-reported falls in univariate analysis. Knowledge that each covariate (except age) is associated with both pain and falls enables results of the multivariate analyses in Chapters 10 and 11 to be interpreted in the context of multiple likely correlations between pain, covariates and falls.

9.7 Chapter summary

This chapter has described the prevalence of self-reported, GP-recorded and HES-recorded falls in thesis sample A and presented univariate analyses of pain and each covariate and their relationship with future self-reported falls in thesis sample B. These findings have been placed in the context of the current evidence base and novel findings that warrant further investigation have been highlighted. An understanding of the associations between covariates and falls has been obtained and more comprehensive multivariate analyses of the relationship between pain and falls can now be undertaken in chapters 10 and 11.

Chapter 10: Pain as a predictor of self-reported falls

10.1 Overview

This chapter examines the relationship between baseline pain status and covariate measurements with future self-reported falls at three and six year follow up. The rationale for the chapter is explained, the methods used to examine the association between multisite pain and self-reported falls are discussed and results presented. Study findings are placed within the current evidence base, novel results are highlighted and implications for the thesis are presented.

10.2 Rationale and chapter objectives

This chapter seeks to examine the role of pain as a predictor of future risk of self-reported falls using a prospective study design. The systematic review and meta-analysis in Chapter 5 highlighted a dearth of good quality prospective studies to establish the risk between multisite pain and falls. This chapter aims to address this knowledge gap by using baseline pain and covariate scores to predict self-reported falls and three and six year follow up. Univariate cross-sectional associations between pain, covariates and baseline future self-reported falls were established in Chapter 9. This chapter moves on to conduct prospective analyses using thesis sample B (containing NorStOP respondents who completed all follow up, who consented to medical record review and who consistently completed the two pain questions) to meet the following objective:

i) to undertake prospective multivariate analysis to establish the relationship between multisite pain and future self-reported falls in the context of putative fall predictors

10.3 Methods

10.3.1 Variable measurements

Pain is analysed using the number of pain sites (0-44) as a continuous measure and the categories of widespreadness (no pain / some pain / widespread pain) as a categorical measure, as described in Chapter 6. Covariates are measured as described in Chapter 6, and baseline self-reported falls is used as an indicator of previous history of fall.

Information on self-reported falls is taken from the NorStOP survey data at three and six year follow up.

10.3.2 Statistical methodology: logistic regression

Logistic regression is used to measure the association between pain and self-reported falls within thesis sample B, as described in Chapter 9. For logistic regression to become clinically useful, multiple predictors of the outcome in question must be considered in the measure of any relationship between the variables of interest. For example, in the case of pain contributing to a risk of falls, it must be considered that sex will also impact upon this relationship, since it is known that women experience more widespread pain than men, as demonstrated

in chapter 9. Multiple variables are considered in the multivariable logistic regression model and the logit of this model is:

$$G(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p$$

where *p* is the number of independent variables under consideration (Hosmer & Lemeshow, 2000). Thus, in multivariable logistic regression models, 'each estimated coefficient provides an estimate of the log odds adjusting for all other variables included in the model' (Hosmer & Lemeshow 2000).

10.3.3 Dealing with potential confounding

Potential confounding must be taken account of during analysis. As discussed in earlier chapters, a confounder is defined as a variable that is related both to the independent variable of interest and the outcome (Bland, 2000). For example, the presence of comorbidities might be a confounder of the relationship between pain and falls since the number of comorbidities might increase the risk of falls and the degree of pain may be influenced by the presence of comorbidities. In logistic regression, confounders are accounted for by adding them into the multivariable logistic regression model so that the potential confounder's influence on the independent variables is also measured.

10.3.4 Interactions

An interaction takes place when the association between the risk factor and outcome varies according to the level of the interaction variable. For example, the association between pain and falls varies according to the number of medications

i.e. the odds ratio for the odds of falling with pain compared to no pain is lower for respondents who do not take medication than for respondents who take more than four medications. In this case, medication would be an 'effect modifier' (Hosmer & Lemeshow, 2000). To test whether variables are 'effect modifiers' rather than confounders, an interaction term must be added to the model. For example, the variable 'medication' would be added as an individual covariate and then combined with 'pain' as an interaction term (commonly notated as medicationXpain). It is possible to then assess if the variable 'medication' is a confounder (i.e. the odds ratio associated with pain changes when 'medication' is added to the model) and if it is also a significant effect modifier (how much the odds ratio of the variable of interest changes when the interaction term is added and whether the p-value associated with the interaction term's coefficient is <0.05). Hence, a variable is considered to be an effect modifier when the interaction term added to the model is clinically meaningful and statistically significant (Hosmer & Lemeshow, 2000). It is important to identify effect modifiers as odds ratios of the variable of interest (pain) must be recalculated.

A pragmatic approach is adopted when testing interactions. Since the independent variable of interest is pain, and univariate analysis of the association between pain and covariates in Chapter 8 found all but age to be statistically significant, interactions between pain and each covariate (except age) are tested. The impact of an interaction is demonstrated using the example of widespread pain and cognitive complaint. The statistically significant association between widespread pain and cognitive complaint means that the effect of pain status differs across different levels of cognitive complaint. When considering only

widespread pain and cognitive complaint as the predictor variables for future falls risk, the equation must include the interaction term and is therefore:

*Falls = ß0 + ß1*widespread pain + ß2*cognitive complaint + ß3*WP*cognitive complaint*

where *ß*0 is the intercept, and *ß* , *ß*2 and *ß*3 are the coefficients that correspond to the odds ratio in the logistic regression model. Thus, the unique effect of pain is not limited to the term 'widespread pain', it also depends on the value of 'cognitive complaint' and the interaction term 'WP*cognitive complaint'. The unique effect of pain is now represented by everything that is multiplied by cognitive impairment. *ß*1 can be considered to indicate the unique effect of widespread pain on falls only when *ß2*cognitive impairment* is equal to zero. Thus, when building the logistic model to take account of possible confounders, modifiers and interaction terms, the *ß* coefficient, or final odds ratio, must be taken from the model that contains the interaction terms to ensure that interactions are accounted for (unless the likelihood ratio test accepts that a smaller model excluding the interaction terms is nested in the bigger model containing the interaction terms, as discussed below).

10.3.5 Model building for logistic regression

There are many strategies for building a logistic regression model and it is important that the final models are clinically meaningful from both biologically plausible and pragmatic viewpoints; this will often mean inclusion of the minimum number of variables. For the purpose of this thesis, multivariable logistic regression models are built to measure the future risk of three and six year self-reported falls associated with baseline pain status and taking account baseline

covariate measures. Firstly, univariate analysis will be undertaken for all variables including pain measures. One method for deciding which variables to include in multivariables analysis is put forward by Mickey and Greenland (1989) who suggest a criteria for model inclusion of univariate analysis p-value of <0.25, after demonstrating that using of a p-value <0.05 tends to miss variables that are known to be important (Mickey & Greenland, 1989; Hosmer & Lemeshow, 2000). However, this analysis will include all covariates, measured according to Chapter 7, since the model must also reflect real-life clinical practice. For example, if all the covariates that do not have significant univariate associations with self-reported falls in prospective analysis are removed from any mathematical modeling, then there would be covariates that have been excluded despite demonstrating their statistically significant relationship with pain status in Chapter 8. The model would no longer reflect real-life as any potential effect modifiers of the pain-falls relationship due to their significant association with pain would be excluded, something that is not possible to do in a clinical scenario. Covariates are therefore added in the following groups to in a stepwise fashion to build models according to the plan in box 10.1.

Interactions are tested and those that are found to be clinically and statistically significant will be added to the model and compared with the model containing all the non-interaction terms using the likelihood ratio test. The likelihood ratio test is used to determine the likelihood that the small model (the model not containing the interactions) is nested within the large model (the model containing the interaction terms); if the likelihood ratio test has a probability of less than 0.05, this means that the likelihood of the small model being nested in the large model is less than

5%, and therefore the large model must be taken as the final model from which to draw conclusions.

Box 10.1: Logistic regression model building

Model 1: unadjusted relationship with pain

Model 2: Model 1 + demographic covariates (full time education status, income adequacy, IMD, occupational class)

Model 3: Model 2 + physical health (BMI, comorbidities, dizziness, vision, hearing)

Model 4: Model 3 + mental health (anxiety, depression, cognitive impairment)

Model 5: Model 4 + medications (total medication count, use of NSAIDs, maximum category of analgesic medication)

Model 6: Model 5 + physical functioning

Model 7: Model 6 + history of baseline self-reported fall

10.3.6 Choice of study sample

The analysis outcomes are i) self-reported fall at three year follow up (yes/ no); and ii) self-reported fall at six year follow up (yes / no). Since the outcome is binary (i.e. there is no option for missing falls data that is due to loss to follow up), thesis sample B (n=4,386) must be used; thesis sample A would have a large number of missing data for three and six year self-reported falls due to loss to follow up at three and six years.

10.4 Results

10.4.1 Baseline pain and covariate measurements and three year self-reported fall

10.4.1.1 Number of pain sites and three year self-reported fall

Table 10.1 presents odds ratios (the beta co-efficient) and 95% CIs for multivariate logistic regression predicting self-reported falls at three year follow up. The table presents results from each step of the model build-up as described in box 10.1, from model 1 (unadjusted) through to model 8 (adjusted for all covariates and statistically significant interaction terms). Statistically significant interaction terms added to model 7 were 'number of pain sites*maximum analgesic category', 'number of pain sites*occupational class', 'number of pain sites*age'. The likelihood ratio test p-value is <0.01, therefore the model containing the interaction terms must be used to interpret odds ratios.

The number of pain sites remains statistically significantly associated with three year self-reported fall across all models; the final model (model 8) gives an odds ratio of 1.12 (1.01-1.24) p=0.04 for the odds of falling for each unit increase in the number of pain sites.

Other covariates that were statistically significant in model 8 once interactions are adjusted for that increased the risk of three year self-reported fall are increasing age (OR 1.04 (1.02-1.05) p=<0.01), cognitive impairment (OR 1.01 (1.01-1.02) p=<0.01), total medication count (OR 1.05 (1.00-1.09) p=0.04) , strong opioids (OR 2.34 (1.31-4.19) p=<0.01) and baseline self-reported falls (OR 2.60 (1.94-3.48) p=<0.01). Covariates statistically significantly associated with reduced odds of falling are non-manual occupation (OR 0.62 (0.46-0.85) p=<0.01) and a CCI score of 2 or more (OR 0.54 (0.33-0.88) p=<0.01).

Table 10.1 Odds ratios (95% CIs) of a self-reported fall at three year follow up according to baseline number of pain sites in a multivariate logistic regression model

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**	**Model 8 n=3,801**
Number of pain sites	**1.06(1.05-1.07)**	**1.06(1.04-1.07)**	**1.05(1.03-1.06)**	**1.03(1.02-1.05)**	**1.03 (1.01-1.04)**	**1.02 (1.01-1.04)**	**1.02 (1.00-1.04)**	**1.12 (1.01-1.24)**
Age (years)		**1.03 (1.01-1.04)**	**1.03(1.01-1.04)**	**1.03(1.01-1.04)**	**1.02(1.01-1.04)**	**1.02(1.01-1.03)**	**1.02 (1.01-1.04)**	**1.04(1.02-1.05)**
Sex: Male		**0.74 (0.60-0.89)**	**0.78 (0.63-0.95)**	**0.74 (0.60-0.92)**	**0.76 (0.61-0.95)**	**0.78 (0.62-0.97)**	0.83 (0.66-1.04)	0.83 (0.66-1.04)
FT Ed >16y: No		**0.96 (0.73-1.28)**	0.97 (0.72-1.30)	1.09 (0.79-1.49)	1.09 (0.79-1.94)	1.06 (0.77-1.45)	1.06 (0.77-1.46)	1.04 (0.75-1.43)
Income adequate		**0.80 (0.65-0.97)**	0.83 (0.67-1.01)	1.05 (0.84-1.31)	1.08 (0.86-1.35)	1.10 (0.88-1.38)	1.07 (0.85-1.34)	1.08 (0.86-1.35)
Occ Class non-manual		**0.74 (0.61-0.91)**	**0.75(0.61-0.93)**	**0.78 (0.63-0.97)**	**0.79 (0.63-0.98)**	**0.77 (0.62-0.97)**	**0.75(0.60-0.94)**	**0.62(0.46-0.85)**
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 referent 0.93 (0.69-1.25) 1.04 (0.77-1.40) 1.19 (0.88-1.62) 1.09 (0.80-1.49)	 referent 0.95 (0.70-1.29) 1.08 (0.79-1.46) 1.23 (0.90-1.68) 1.04 (0.75-1.44)	 referent 0.97 (0.70-1.34) 1.12 (0.81-1.54) 1.28 (0.93-1.78) 1.00 (0.71-1.41)	 referent 0.96 (0.70-1.33) 1.07 (0.78-1.49) 1.25 (0.90-1.73) 0.98 (0.69-1.38)	 referent 0.96 (0.69-1.33) 1.08 (0.78-1.50) 1.23 (0.89-1.72) 1.00 (0.70-1.41)	 referent 0.94 (0.68-1.31) 1.06 (0.76-1.48) 1.20 (0.76-1.48) 0.98 (0.69-1.39)	 referent 0.94 (0.67-1.30) 1.06 (0.76-1.47) 1.18 (0.84-1.65) 0.97 (0.68-1.38)
Dizzy: Yes			**1.72 (1.38-2.15)**	**1.34 (1.05-1.71)**	**1.30 (1.02-1.67)**	**1.31 (1.02-1.68)**	1.23 (0.95-1.58)	1.23 (0.96-1.58)
Hearing deficit: Yes			0.93 (0.71-1.23)	0.90 (0.67-1.21)	0.91 (0.68-1.23)	0.91 (0.68-1.22)	0.90 (0.67-1.22)	0.91 (0.67-1.23)
Visual deficit: Yes			1.24 (0.96-1.59)	1.14 (0.88-1.49)	1.13(0.86-1.48)	1.15(0.88-1.50)	1.11 (0.85-1.46)	1.14 (0.86-1.49)
CCI score 0 1 2-8			 referent 0.84 (0.64-1.12) 0.80 (0.53-1.20)	 referent 0.85(0.63-1.14) 0.69(0.44-1.09)	 referent 0.76 (0.56-1.04) **0.55 (0.34-0.89)**	 referent 0.76(0.56-1.04) **0.54 (0.33-0.88)**	 referent 0.77 (0.56-1.05) **0.53 (0.33-0.87)**	 referent 0.75(0.55-1.03) **0.54 (0.33-0.88)**
BMI			**1.03(1.01-1.05)**	**1.03(1.01-1.05)**	**1.03(1.01-1.05)**	**1.03(1.01-1.05)**	**1.03(1.01-1.05)**	1.02 (1.00-1.04)

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**	**Model 8 n=3,801**
Depression				1.03 (0.99-1.07)	1.02 (0.98-1.06)	1.01 (0.97-1.06)	1.02 (0.97-1.06)	1.01 (0.97-1.06)
Anxiety				1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.02 (0.99-1.06)	1.02 (0.99-1.06)	1.02 (0.99-1.06)
Cognitive complaint				**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**
Total medication					**1.05 (1.00-1.09)**	1.04 (1.00-1.09)	1.04 (1.00-1.09)	**1.05 (1.00-1.09)**
Analgesics None Basic Weak op. Mod. op. Strong op. V.strong op.					 Referent 1.04 (0.68-1.59) 1.22 (0.78-1.89) 1.26 (0.84-1.90) **1.01 (1.01-1.02)** 1.60 (0.25-10.1)	 Referent 1.05 (0.68-1.61) 1.21 (0.78-1.88) 1.20 (0.79-1.82) **1.64 (1.07-2.49)** 1.51 (0.24-9.59)	 Referent 1.09 (0.71-1.68) 1.22 (0.78-1.91) 1.17 (0.76-1.78) **1.56 (1.01-2.39)** 1.32 (0.20-8.63)	 Referent 1.16(0.76-1.79) 1.43 (0.89-2.30) 1.54 (0.94-2.54) **2.34 (1.31-4.19)** 2.39 (0.29-19.64)
NSAIDs: Yes					0.86 (0.62-1.19)	0.87 (0.63-1.20)	0.84 (0.60-1.17)	0.81 (0.58-1.13)
Physical functioning No problem A little A lot						 Referent 1.17 (0.86-1.60) 1.21 (0.80-1.83)	 Referent 1.15 (0.84-1.57) 1.04 (0.68-1.60)	 Referent 1.14 (0.84-1.55) 1.13 (0.74-1.73)
Previous fall: Yes							**2.65(1.97-3.54)**	**2.60 (1.94-3.48)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; Model 8: Model 7 & adjustment for all covariates and statistically significant interaction terms). OR = odds ratios; 95% CI = 95% confidence interval; where $p<0.05$, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2^{nd} least = 2^{nd} least deprived, mid dep. = middle deprivation category, 2^{nd} most = 2^{nd} most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates, v. strong op. = very strong opiates. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

10.4.2.2 Widespread pain and three year self-reported fall

Table 10.2 presents odds ratios (the beta co-efficient) and 95% CIs for logistic regression predicting self-reported falls at three year follow up. The table presents results from each step of the model build-up, from model 1 (unadjusted) through to model 7 (adjusted for all covariates). There were no statistically significant interaction terms, thus model 7 is the final model containing all the covariates.

The unadjusted association between 'some pain' and 'widespread pain' is statistically significantly associated with three-year self-reported falls; however the statistical significance is lost for 'some pain' when demographics are added to the model, and is lost for 'widespread pain' when physical functioning is added to the model. The final models report, for 'some pain' odds ratio 1.00 (0.75-1.33) p=0.98 and for 'widespread pain' OR 1.27 (0.92-1.75) p=0.14.

Covariates that statistically significantly increase the odds of three year self-reported falls in model 7 are age (OR 1.02 (1.01-1.04) p=<0.01), BMI (OR 1.03 (1.00-1.05) p=0.02), strong opioids (OR 1.61 (1.05-2.47) p=0.03) and previous history of self-reported fall (OR 2.70 (2.01-3.61) p=<0.01). The greatest predictor of three year self-reported fall is previous falls history, where the odds of falling in those reporting baseline falls is two and a half times that of those who did not report baseline falls. Covariates that reduce the odds of falling in model 7 are non-manual work (OR 0.76 (0.61-0.95) p=0.02) and a Charlson score of 2 or more comorbidities (OR 0.53 (0.32-0.87) p=0.01).

Table 10.2 Odds ratios (95% CIs and p-values) of a self-reported fall at three year follow up according to baseline pain widespreadness in a multivariate logistic regression model

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**
No pain Some pain Widespread	Referent **1.54 (1.20-1.99)** **2.96 (2.31-3.80)**	Referent **1.39 (1.06-1.80)** **2.57 (1.97-3.35)**	Referent 1.25 (0.96-1.63) **2.14 (1.62-2.82)**	Referent 1.14 (0.85-1.50) **1.60 (1.18-2.16)**	Referent 1.06 (0.80-1.41) **1.41 (1.03-1.92)**	Referent 1.03 (0.77-1.37) 1.32 (0.96-1.81)	Referent 1.00 (0.75-1.33) 1.27 (0.92-1.75)
Age (years)		**1.03 (1.02-1.04)**	**1.03 (1.01-1.04)**	**1.03 (1.01-1.04)**	**1.02 (1.01-1.04)**	**1.02 (1.01-1.03)**	**1.02 (1.01-1.04)**
Sex: Male		**0.72 (0.59-0.87)**	**0.77 (0.63-0.94)**	**0.73 (0.58-0.90)**	**0.76 (0.61-0.94)**	**0.77 (0.62-0.97)**	**0.83 (0.66-1.03)**
FT Ed >16y: No		0.97 (0.73-1.29)	0.98 (0.74-1.31)	1.10 (0.81-1.56)	1.10 (0.80-1.50)	1.07 (0.78-1.46)	1.07 (0.78-1.47)
Income adequate		**0.75 (0.62-0.91)**	**0.80 (0.65-0.97)**	1.03 (0.83-1.29)	1.07 (0.85-1.33)	1.09 (0.87-1.37)	1.06 (0.84-1.33)
Occ Class non-manual		**0.77 (0.63-0.95)**	**0.78 (0.63-0.96)**	**0.80 (0.64-1.00)**	**0.80 (0.64-1.00)**	**0.79 (0.63-0.98)**	**0.76 (0.61-0.95)**
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 Referent 0.94 (0.70-1.27) 1.06 (0.78-1.43) 1.25 (0.92-1.69) **1.14 (0.59-0.87)**	 Referent 0.96 (0.70-1.30) 1.09 (0.80-1.48) 1.27(0.93 -1.73) 1.07 (0.77-1.47)	 Referent 0.98 (0.71-1.35) 1.13 (0.82-1.56) 1.30 (0.94-1.80) 1.02 (0.72-1.43)	 Referent 0.97 (0.70-1.34) 1.08 (0.78 1.50) 1.26 (0.91-1.75) 0.99 (0.70-1.40)	 Referent 0.97 (0.70-1.34) 1.08 (0.78-1.50) 1.24 (0.89-1.73) 1.00 (0.71-1.42)	 Referent 0.94 (0.68-1.31) 1.07 (0.77-1.48) 1.21 (0.86-1.69) 0.99 (0.69-1.40)
Dizzy: Yes			**1.81 (1.46-2.25)**	**1.39 (1.09-1.77)**	**1.34 (1.05-1.71)**	**1.34 (1.04-1.72)**	1.25 (0.97-1.60)
Hearing deficit: Yes			0.94 (0.71-1.23)	0.90 (0.68-1.21)	0.92 (0.68-1.23)	0.91 (0.68-1.23)	0.90 (0.67-1.22)
Visual deficit: Yes			1.27 (0.99-1.63)	1.16 (0.89-1.51)	1.14 (0.88-1.50)	1.16 (0.89-1.53)	1.12 (0.86-1.48)
CCI score 0 1 2-8			 Referent 0.89 (0.67-1.18) 0.81 (0.53-1.21)	 Referent 0.88 (0.65-1.18) 0.70 (0.45-1.09)	 Referent 0.78 (0.57-1.06) **0.54 (0.33-0.88)**	 Referent 0.77 (0.57-10.6) **0.53 (0.57-0.87)**	 Referent 0.78 (0.57-1.07) **0.53 (0.32-0.87)**
BMI			**1.03 (1.01-1.05)**	1.02 (1.00-1.05)	**1.03 (1.01-1.05)**	**1.03(1.00-1.05)**	**1.03 (1.00-1.05)**

Covariate OR (95% CI)	Model 1 n=4,386	Model 2 n=4,089	Model 3 n=4,015	Model 4 n=3,830	Model 5 n=3,830	Model 6 n=3,801	Model 7 n=3,801
Depression				1.04 (1.00-1.08)	1.02 (0.98-1.07)	1.02 (0.97-1.06)	1.02 (0.97-1.06)
Anxiety				1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.02 (0.99-1.06)	1.02 (0.99-1.06)
Cognitive complaint				**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**	**1.02 (1.01-1.02)**	1.01 (1.00-1.02)
Total medication					**1.05 (1.00-1.09)**	1.04 (1.00-1.02)	1.04 (1.00-1.09)
Analgesics None Basic Weak op Mod. op Strong op V. strong op					 Referent 1.05 (0.68-1.60) 1.24 (0.80-1.92) 1.31 (0.88-1.97) **1.82 (1.21-2.73)** 1.93 (0.31-12.0)	 Referent 1.06 (0.69-1.63) 1.22 (0.78-1.91) 1.23 (0.81-1.87) **1.71 (1.13-2.60)** 1.75 (0.28-10.9)	 Referent 1.10 (0.71-1.69) 1.23 (0.78-1.93) 1.20 (0.78-1.83) **1.61 (1.05-2.47)** 1.46 (0.22-9.83)
NSAIDs: Yes					1.41 (1.01-1.99)	0.89 (0.65-1.23)	0.86 (0.62-1.19)
Physical functioning No problem A little A lot						 Referent 1.22 (0.90-1.66) 1.30 (0.86-1.96)	 Referent 1.18 (0.87-1.61) 1.10 (0.73-1.68)
Previous fall: Yes							**2.70 (2.01-3.61)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; OR = odds ratios; 95% CI = 95% confidence interval; where $p<0.05$, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2^{nd} least = 2^{nd} least deprived, mid dep. = middle deprivation category, 2^{nd} most = 2^{nd} most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates, v. strong op. = very strong opiates. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

10.4.2 Baseline pain and covariate measurements and six year self-reported fall

10.4.3.1 Number of pain sites and six year self-reported fall

Table 10.3 presents odds ratios (the beta co-efficient) and 95% CIs for logistic regression predicting self-reported falls at six year follow up. The table presents results from each step of the model build-up, from model 1 (unadjusted) through to model 7 (adjusted for all covariates). There were no statistically significant interactions to be included in the model, thus model 7 provides odds ratios to be interpreted for results.

The number of pain sites remains statistically significantly associated with future six year self-reported fall across all models, with the level of significance changing when physical functioning and baseline self-reported fall are added to the analysis and model 7 giving an odds ratio of 1.02 (1.00-1.03), p=0.04.

Covariates that statistically significantly increased the odds of reporting a six year self-reported fall once all covariates are adjusted for are age (OR 1.03 (1.02-1.04) p=<0.01), dizziness (OR 1.69 (1.34-2.13) p=<0.01) , cognitive impairment (OR 1.01 (1.00-1.01) p=<0.01), physical functioning (a little limitation OR 1.79 (1.35-2.38, p=<0.01; a lot of limitation OR 1.84 (1.25-2.71) p=<0.01) and baseline self-reported falls (OR1.94 (1.45-2.59), p=<0.01). Adequate income reduced the odds of reporting a six year fall (OR 0.79 (0.64-0.98) p=0.03).

Table 10.3 Odds ratios (95% CIs and p-values) of a self-reported fall at six year follow up according to baseline number of pain sites in a multivariate logistic regression model

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**
Number of pain sites	**1.06 (1.05-1.07)**	**1.06 (1.04-1.07)**	**1.04 (1.03-1.06)**	**1.03 (1.02-1.05)**	**1.03 (1.01-1.04)**	**1.02 (1.00-1.04)**	**1.02 (1.00-1.03**)
Age (years)		**1.04 (1.03-1.05)**	**1.04 (1.03-1.05)**	**1.04 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.02-1.05)**
Sex: Male		**0.77 (0.64-0.93)**	**0.81 (0.66-0.98)**	**0.77 (0.63-0.95)**	**0.80 (0.65-0.98)**	**0.81 (0.66-1.00)**	0.84 (0.68-1.04)
FT Ed >16y: No		**0.74 (0.57-0.96)**	**0.75 (0.58-0.98)**	0.79 (0.60-1.04)	0.80 (0.60-1.05)	0.77 (0.59-1.02)	0.76 (0.59-1.02)
Income adequate		**0.67 (0.56-0.81)**	**0.70 (0.58-0.85)**	**0.76 (0.62-0.93)**	**0.76 (0.62-0.93)**	0.81 (0.65-1.00)	**0.79 (0.64-0.98)**
Occ Class non-manual		0.93 (0.76-1.13)	0.95 (0.77-1.16)	0.95 (0.77-1.17)	0.95 (0.77-1.17)	0.95 (0.77-1.17)	0.94 (0.76-1.16)
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 Referent 1.20 (0.91-1.60) 1.19 (0.89-1.59) 1.08 (0.79-1.47) 1.30 (0.96-1.77)	 Referent 1.25 (0.94-1.67) 1.20 (0.89-1.62) 1.08 (0.79-1.47) 1.22 (0.89-1.67)	 Referent **1.36 (1.01-1.83)** 1.20 (0.88-1.64) 1.10 (0.79-1.52) 1.19 (0.86-1.66)	 Referent **1.36 (1.01-1.83)** 1.18 (0.86-1.61) 1.09 (0.79-1.52) 1.19 (0.86-1.65)	 Referent 1.34 (0.99-1.81) 1.17 (0.86-1.60) 1.07 (0.77-1.48) 1.13 (0.81-1.58)	 Referent 1.32 (0.98-1.78) 1.16 (0.85-1.58) 1.05 (0.75-1.45) 1.11 (0.80-1.55)
Dizzy: Yes			**2.08 (1.69-2.57)**	**1.81 (1.44-2.27)**	**1.78 (1.42-2.24)**	**1.76 (1.40-2.21)**	**1.69 (1.34-2.13)**
Hearing deficit: Yes			0.90 (0.69-1.17)	0.87 (0.66-1.14)	0.88 (0.67-1.16)	0.86 (0.65-1.14)	0.85 (0.64-1.13)
Visual deficit: Yes			1.23 (0.97-1.57)	1.21 (0.94-1.55)	1.22 (0.95-1.57)	1.25 (0.97-1.62)	1.23 (0.95-1.59)
CCI score 0 1 2-8			 Referent 0.88 (0.68-1.16) 1.18 (0.82-1.70)	 Referent 0.91 (0.69-1.20) 1.08 (0.73-1.59)	 Referent 0.87 (0.65-1.16) 0.96 (0.63-1.44)	 Referent 0.83 (0.62-1.11) 0.89 (0.59-1.36)	 Referent 0.83 (0.62-1.12) 0.90 (0.59-1.36)
BMI			1.01 (1.00-1.03)	1.01 (0.99-1.03)	1.01 (0.98-1.03)	1.00 (0.98-1.02)	1.00 (0.98-1.02)

Covariate OR (95% CI)	Model 1 n=4,386	Model 2 n=4,089	Model 3 n=4,015	Model 4 n=3,830	Model 5 n=3,830	Model 6 n=3,801	Model 7 n=3,801
Depression				**1.05 (1.01-1.09)**	1.04 (1.00-1.08)	1.03 (0.98-1.07)	1.03 (0.99-1.07)
Anxiety				0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)
Cognitive complaint				**1.01 (1.01-1.02)**	**1.01 (1.00-1.02)**	**1.01 (1.00-1.02)**	**1.01 (1.00-1.01)**
Total medication					1.03 (0.99-1.07)	1.02 (0.98-1.06)	1.02 (0.98-1.06)
Analgesics None Basic Weak op Mod. op Strong op V. strong op					 Referent 0.93 (0.62-1.40) 1.14 (0.75-1.73) 1.15 (0.78-1.70) **1.54 (1.03-2.29)** 0.60 (0.06-5.79)	 Referent 0.90 (0.59-1.35) 0.95 (0.62-1.46) 0.97 (0.65-1.45) 1.27 (0.85-1.92) 0.47 (0.05-4.59)	 Referent 0.91 (0.60-1.37) 0.95 (0.62-1.47) 0.95 (0.63-1.42) 1.23 (0.81-1.85) 0.44 (0.05-4.18)
NSAIDs: Yes					1.30 (0.98-1.74)	1.28 (0.96-1.72)	1.58 (0.94-1.70)
Physical functioning No problem A little A lot						 Referent **1.81 (1.37-2-40)** **2.02 (1.38-2.96)**	 Referent **1.79 (1.35-2.38)** **1.84 (1.25-2.71)**
Previous fall: Yes							**1.94 (1.45-2.59)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; OR = odds ratios; 95% CI = 95% confidence interval; where $p<0.05$, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates, v. strong op. = very strong opiates. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

11.4.3.2 Widespread pain measure and six year self-reported fall

Table 10.4 presents odds ratios (the beta co-efficient) and 95% CIs for logistic regression predicting self-reported falls at six year follow up. The table presents results from each step of the model build-up, from model 1 (unadjusted) through to model 7 (adjusted for all covariates). Statistically significant interactions included were 'widespread pain*hearing impairment'. 'The likelihood ratio test p-value is 0.10, therefore model 7 can be accepted rather than the model including the interaction terms.

'Some pain' is statistically significantly related to six year self-reported falls until physical functioning is added to the model; model 7 gives an odds ratio of 1.22 (0.93-1.61) p=0.15 for 'some pain' compared to no pain for risk of six year self-reported fall. 'Widespread pain' remains statistically significantly related to six year self-reported fall across all models (model 7 OR 1.43 (1.06-1.95) p=0.02).

Covariates that statistically significantly increase the odds of reporting a six year self-reported fall once all covariates are adjusted for are increasing age (OR 1.03 (1.02-1.04) p=<0.01) , dizziness (OR 1.70 (1.35-2.140 p=<0.01), cognitive impairment (OR 1.01 (1.00-1.01) p=<0.01), physical functioning (a little limitation OR 1.81 (1.36-2.39) p=<0.01; a lot of limitation OR 1.91 (1.31-2.80) p=<0.01) and baseline self-reported falls (OR 1.96 (1.47-2.61) p=<0.01). Adequate income reduces the odds of reporting a six year self-reported fall (OR 0.78 (0.63-0.97) p=0.03).

Table 10.4 Odds ratios (95% CIs and p-values) of a self-reported fall at six year follow up according to baseline pain widespreadness in a multivariate logistic regression model

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**
No pain Some pain Widespread	Referent **1.63 (1.28-2.06)** **2.90 (2.27-3.79)**	Referent **1.58 (1.23-2.03)** **2.60 (2.00-3.36)**	Referent **1.44 (1.11-1.86)** **2.08 (1.59-2.73)**	Referent **1.40 (1.08-1.83)** **1.83 (1.37-2.44)**	Referent 1.31 (1.00-1.71) **1.60 (1.19-2.16)**	Referent 1.24 (0.95-1.63) **1.46 (1.08-1.99)**	Referent 1.22 (0.93-1.61) **1.43 (1.06-1.95)**
Age (years)		**1.04 (1.03-1.05)**	**1.04 (1.03-1.05)**	**1.04 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.2-1.04)**	**1.03 (1.02-1.04)**
Sex: Male		**0.75 (0.62-0.90)**	**0.79 (0.65-0.96)**	**0.76 (0.62-0.93)**	**0.79 (0.64-0.97)**	**0.80 (0.65-0.99)**	0.84 (0.68-1.03)
FT Ed >16y: No		**0.75 (0.58-0.97)**	**0.76 (0.59-0.99)**	0.80 (0.01-1.05)	0.80 (0.61-1.06)	0.77 (0.59-1.02)	0.77 (0.59-1.02)
Income adequate		**0.63 (0.52-0.77)**	**0.67 (0.55-0.82)**	**0.75 (0.61-0.92)**	**0.76 (0.62-0.93)**	**0.80 (0.65-0.99)**	**0.78 (0.63-0.97)**
Occ Class non-manual		0.97 (0.79-1.17)	0.97 (0.80-1.19)	0.91 (0.79-1.19)	0.97 (0.79-1.19)	0.96 (0.78-1.19)	0.95 (0.77-1.17)
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 Referent 1.22 (0.92-1.62) 1.22 (0.91-1.64) 1.14 (0.84-1.54) **1.38 (1.02-1.86**	 Referent 1.26 (0.94-1.68) 1.23 (0.91-1.65) 1.11 (0.81-1.52) 1.26 (0.92-1.72	 Referent **1.37 (1.02-1.85)** 1.22 (0.89-1.66) 1.13 (0.81-1.56) 1.21 (0.88-1.68	 Referent **1.37 (1.02-1.85)** 1.19 (0.87-1.63) 1.11 (0.80-.154) 1.20 (0.87-1.67	 Referent 1.35 (1.00-1.82) 1.18 (0.86-1.61) 1.08 (0.78-1.51) 1.14 (0.81-1.58)	 Referent 1.32 (0.98-1.79) 1.16 (0.85-1.59) 1.06 (0.76-1.47) 1.12 (0.80-1.56)
Dizzy: Yes			**2.20 (1.79-2.70)**	**1.86 (1.49-2.32)**	**1.82 (1.45-2.28)**	**1.78 (1.41-2.24)**	**1.70 (1.35-2.14)**
Hearing deficit: Yes			0.90 (0.69-1.17)	0.86 (0.66-1.13)	0.88 (0.67-1.16)	0.86 (0.65-1.14)	0.85 (0.64-1.13)
Visual deficit: Yes			1.27 (1.00-1.61)	1.23 (0.95-1.57)	1.23 (0.96-1.59)	1.26 (0.98-1.63)	1.24 (0.96-1.60)
CCI score 0 1 2-8			 Referent 0.92 (l.71-1.72) 1.20 (0.84-1.72)	 Referent 0.93 (0.71-1.23) 1.09 (0.74-1.60	 Referent 0.86 (0.66-1.18) 0.96 (0.64-1.45)	 Referent 0.84 (0.63-1.12) 0.89 (0.59-1.36)	 Referent 0.84 (0.63-1.13) 0.90 (0.59-1.36)
BMI			1.02 (1.00-1.04)	1.01 (0.99-1.03)	1.01 (0.98-1.03)	1.00 (0.98-1.02)	1.00 (0.98-1.02)

Covariate OR (95% CI)	**Model 1 n=4,386**	**Model 2 n=4,089**	**Model 3 n=4,015**	**Model 4 n=3,830**	**Model 5 n=3,830**	**Model 6 n=3,801**	**Model 7 n=3,801**
Depression				**1.06 (1.02-1.10)**	**1.04 (1.00-1.09)**	1.03 (0.99-1.07)	1.03 (0.99-1.07)
Anxiety				0.98 (0.94-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)
Cognitive complaint				**1.01 (1.01-1.02)**	**1.01 (1.01-1.02)**	**1.01 (1.01-1.02)**	**1.01 (1.00-1.01)**
Total medication					1.03 (0.99-1.07)	1.02 (0.98-1.06)	1.02 (0.98-1.06)
Analgesics None Basic Weak op Mod. op Strong op V. strong op					 Referent 0.92 (0.61-1.38) 1.14 (0.75-1.73) 1.17 (0.79-1.72) **1.61 (1.09-2.38)** 0.74 (0.08-6.96)	 Referent 0.88 (0.58-1.33) 0.94 (0.61-1.45) 0.97 (0.65-1.45) 1.30 (0.87-1.95) 0.53 (0.06-5.09)	 Referent 0.90 (0.59-1.35) 0.94 (0.61-1.45) 0.94 (0.61-1.45) 1.24 (0.83-1.87) 0.48 (0.50-4.51)
NSAIDs: Yes					1.32 (0.99-1.76)	1.29 (0.96-1.72)	1.27 (0.94-1.70)
Physical functioning No problem A little A lot						 Referent **1.83 (1.39-2.42)** **2.11 (1.45-3.08)**	 Referent **1.81 (1.36-2.39)** **1.91 (1.31-2.80)**
Previous fall: Yes							**1.96 (1.47-2.61)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; OR = odds ratios; 95% CI = 95% confidence interval; where $p<0.05$, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates, v. strong op. = very strong opiates. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

10.4.3 Multivariate analysis: summary

An increasing number of pain sites statistically significantly increased the odds of self-reported falls at three and six years with odds ratios of 1.12 (1.01-1.24) p=0.04 and 1.03 (1.02-1.04) p=<0.01 respectively. Each additional pain site conferred a 12% increased odds of falling at three years and a 3% increased odds of falling at six years.

Widespread pain, as measured using the widespread pain measure, did not statistically significantly predict three year self-reported fall; the presence of widespread pain did however statistically significantly increase the odds of a self-reported fall at six years by 43% compared to those with no pain (OR 1.43 (1.06-1.95) p=0.02).

Table10.5 presents the statistically significant covariates in the final models for three and six year falls. The presence of dizziness and limitation in physical functioning were statistically significantly associated with increased odds of self-reported fall at six years but not at three years. Increasing BMI, increasing total medication count and a prescription for strong opioids were statistically significantly associated with increased odds of a three year self reported fall but not six year self-reported fall.

Table 10.5 Multivariable logistic regression of the relationship between multisite pain and future self-reported fall: statistically significant predictors at three year and six year follow up

Three year self-reported fall	Six year self-reported fall
Covariates increasing the odds of falling:	
Number of pain sites	Number of pain sites
Increasing age	Increasing age
Increasing BMI	Presence of dizziness
Increased cognitive complaint score	Increasing cognitive complaint
Increased total medication count	Limitation in physical functioning
Strong opioid prescription	History of baseline self-reported fall
History of baseline self-reported fall	
Covariates reducing the odds of falling:	
Non-manual occupation	Adequate income
Higher multimorbidity score	

10.5 Discussion

10.5.1 Summary of findings

Univariate analysis of covariates and future falls has found that increasing age, higher deprivation levels, a higher BMI, the presence of dizziness, hearing difficulty and vision impairment, two or more CCI comorbidities, increasing anxiety, increasing depression and increasing cognitive complaint scores, increasing total medication count, opioid analgesics, NSAID use, limitation in physical functioning and baseline self-reported fall were all associated with a statistically significant increased odds of a future three, or six, year self-reported fall. Being male and adequate income statistically significantly reduced the odds of reporting a fall at three and six years.

An increasing number of pain sites statistically significantly increased the odds of three, or six, year self-reported fall when all covariates were included in the logistic regression model. This means that an increasing number of pain sites confer an increased risk of falling even when traditional falls risk factors and other putative influencing covariates are accounted for.

The presence of widespread pain is also associated with statistically significantly increased odds of falling at six years when all covariates were included in the logistic regression model, thus meaning that widespread pain confers an additional risk of future self-reported falls in excess of that predicted by traditional falls risk factors and other putative influencing covariates are accounted for.

10.5.2 How it fits into current literature and what is new

Referring back to the systematic review and meta-analysis, where all of the included studies had self-reported falls as outcomes, the adjusted pooled effect estimate for the presence of multisite pain and falls was an odds ratio of 1.56 (1.40-1.75); the unadjusted pooled effect estimate for prospective studies only was 1.70 (1.49-1.94). The adjusted odds ratio for the number of pain sites and three year and six falls in this thesis are 1.12 (1.01-1.24) and 1.03 (1.02-1.04) respectively. The odds ratio for widespread pain and three and six year falls are 1.27 (0.92-1.75) and 1.43 (1.06-1.95) respectively. The effect estimates from this thesis are lower than that derived in the meta-analysis. This may be due to the highly adjusted effect estimates in this thesis. The meta-analysis demonstrated that, when adjusting for multiple variables, the pooled odds ratio reduced from 1.83 (1.54-2.19). This is unsurprising since, the more variables that are added to

the model, the more variables are available to explain effect size and the lower each individual variable's contribution becomes.

Other variables that were statistically significantly associated with increased odds of future self-reported fall in final adjusted models were expected and in line with traditional falls risk factors that are addressed in current falls prevention guidelines. For example, the multifactorial risk assessment recommended by NICE (2013) explicitly advises assessment of cognitive functioning, medication review, the presence of dizziness, physical functioning and history of previous falls. BMI assessment is not included in falls guidelines, and the magnitude of increased odds per unit increase in BMI of 1.03 (1.00-1.05) with the confidence interval including 1.00 is unlikely to be clinically significant.

This study has found that a higher multimorbidity score (scoring 2 or more on the CCI) is associated with reduced odds of future three year self-reported fall. This is the first study to demonstrate this protective effect and is most likely due to the composition of thesis sample B. This sample has been derived from thesis sample A and includes those who are healthy enough to complete six years of study follow up with consistent pain data. This healthy cohort effect may explain this apparent protective effect if these higher-scoring respondents do not have any other falls risk factors, for example, they do not have a baseline self-reported fall, are not dizzy and do not take many medications. Alternatively, it may be that those with multimorbidities are less able to move about and have few opportunities to fall though this is unlikely given the derivation of thesis sample B.

10.5.3 Strengths

The major strength of this study is the inclusion of multiple covariates in analysis to enable the results to be as clinically relevant as possible. Traditional falls risk factors and covariates known to be associated with pain are all included to ensure that any relationships beyond pain and falls are incorporated into the analysis. Interactions have also been tested and included in the final models where necessary, again increasing the clinical relevance of this result.

The study uses prospective falls data, which means that causality can be inferred from the effect estimate. Thus, it is possible to conclude that multisite pain does incur an additional risk of future self-reported fall in addition to traditional falls risk factors. This is a more clinically useful conclusion than that derived from cross-sectional data, where it is not possible to establish a temporal relationship.

10.5.4 Limitations

The problems around the self-reported measure including recall bias and the limited three month recall as discussed in Chapter 9 are also relevant to this analysis.

Furthermore, although this analysis has considered 19 covariates, there are a few known falls risk factors that are not taken account of due to no data being available. These include assessments of home hazards and urinary incontinence (NICE, 2013) and measures of gait, balance, mobility and strength such as those tests used by Leveille et al (2009) (chair stands test, gait speed, balance) and Stubbs et al (2015) (Timed Up and Go test). No information on another

established risk factor, fear of falling, was available (Friedman et al, 2002). Adding these factors to the model may attenuate the risk of future falls attributed to pain and render the effect estimate associated with pain statistically non-significant. The covariates used in this analysis all consist of information easily, and efficiently, available to GPs, thus this analysis is clinically useful as GPs will have information about these covariates to hand. Assessing urinary incontinence and fear of falling is quick and possible to undertake in a ten minute GP consultation; formal measures of gait, balance, mobility and strength will be more challenging to complete within a standard consultation and including these in the model will render it less clinically useful.

10.5.5 Informing the thesis

This analysis has shown that multisite pain, when measured as number of pain sites and as widespread pain, is associated with adjusted increased odds of future self-reported falls. Given the potential for recall bias and subsequent misclassification of self-reported fallers leading to an underestimate of self-reported falls prevalence, the estimated effect size could be an underestimate of the true effect size in the general population of older adults.

A prospective analysis will now be undertaken using GP and HES-recorded falls as the outcome measure to examine whether multisite pain also confers a statistically significant risk of health-care associated falls.

10.5.6 Chapter summary

This chapter has examined the role of pain as a predictor of future risk of self-reported falls using a prospective study design. The knowledge gap highlighted by the systematic review and meta-analysis has been addressed and new evidence that multisite pain confers an additional risk of future self-reported falls even when adjusted for multiple covariates that have known associations with pain and falls has been generated by this thesis. The next chapter will examine the relationship between multisite pain and future GP or HES-recorded fall.

Chapter 11: Pain as a predictor of falls requiring primary and secondary health care utilisation

11.1 Overview

This chapter explores the relationship between baseline pain status and covariate measurements with future GP and HES-recorded falls. The rationale for the chapter is explained, methods are outlined and results are presented and summarised. A discussion highlights key findings, strengths and limitations of the study and implications for future clinical practice are proposed.

11.2 Rationale and chapter objectives

This chapter seeks to examine the role of multisite pain as a predictor of future risk of falls requiring primary health care utilisation (GP-recorded fall) and falls requiring secondary health care utilisation (HES-recorded fall) using a prospective study design. The systematic review and meta-analysis in Chapter 5 highlighted a lack of evidence around pain as a risk factor for falls and a paucity of large prospective studies to examine pain as a predictor of future fall risk. This chapter aims to address this knowledge gap by using baseline pain and covariate measurements to predict future risk of GP or HES-recorded falls. Survival analysis is used to analyse the data in thesis sample A (n=11,375, this sample contains NorStOP baseline responders who consented to further medical record review and answered the pain questions consistently) to meet the following objectives:

i) to undertake prospective multivariate analysis to establish the relationship between multisite pain and future GP-recorded falls;

ii) to undertake prospective multivariate analysis to establish the relationship between multisite pain and future HES-recorded falls

11.3 Methods

11.3.1 Variable measurements

Pain is analysed using the number of pain sites as a continuous measure and the categories of widespreadness (no pain / some pain / widespread pain) as a categorical measure, as described in Chapter 6. Covariates are all measured as described in Chapter 6 and previous falls history is considered using self-reported falls at baseline.

11.3.2 Falls

GP-recorded and HES-recorded falls are used as a binary outcome (yes/no) according to 'ever fallen' status for GP or HES recorded falls i.e. respondents who have had one or more GP or HES recorded falls.

11.3.3 A note on time periods

The time period for this analysis matches that used in Chapter 10. The time period begins at the start of the corresponding NorStOP cohort baseline survey mail out and ends at the end of the NorSTOP3 six year follow up mail out, except for respondents who did not complete three year follow up where their study period ends at the end of their corresponding NorStOP three year follow up mail out period. The time that respondents spend in the study therefore differs according to the specific NorStOP cohort and three year follow up response. Thus, respondents in NorStOP1 who complete follow up surveys will have data over ten years, those in NorStOP3 who complete all follow up surveys will have

data over six years and those in any of the NorStOP cohorts who do not complete three year follow up will have their data collected over three years. The implications of these differences are explored in this chapter's discussion.

11.3.4 Cox's proportional hazard regressions

Cox proportional hazards regression enables time to an event to be measured. For example, time from exposure (e.g. smoking) to death (e.g. from cancer), or from treatment (e.g. chemotherapy) to disease recurrence (e.g. breast cancer). Hence this technique is often referred to as 'survival analysis' although it is commonly used when mortality is not the outcome of interest. In the thesis, it is used to measure the risk of time to first fall and to investigate whether that time to first fall is different across different pain exposures. This technique enables the effect of predictor covariates (for example, pain, depression, comorbidity) upon the outcome (falls) to be measured. Continuous, binary and categorical data can be used in analysis as measurements are logarithmically transformed to enable a linear relationship between covariates and outcome to be measured (Peacock J & Peacock P, 2010). After adjusting for all covariates in the model, the analysis gives regression coefficients for each covariate and the time-to-event fall outcome and these are back-transformed to provide an effect measurement as a hazard ratio. For example, if the time to first fall is less for those with widespread pain compared to those reporting some pain or no pain, then the hazard ratio for falling would be greater in the widespread pain group. Further details on how the data is prepared to enable survival analysis are provided in Appendix 9.

11.3.4.1 Testing univariate associations

Prior to running the Cox regression, investigation of each covariate's relationship with time-to-fall is necessary to establish univariate associations within the data that has been flagged or 'set' as time series data. As with previous analyses, all covariates will be added to the Cox proportional hazard model to ensure clinical practice is reflected as far as possible. Univariate analysis for categorical variables will use the log-rank test for equality of survivor functions and generation of Kaplan-Meier curves to assess relationship with time to first fall event. The crude relationship of continuously measured covariates is measured using the Cox proportional hazard model with a single continuous predictor variable and as such may yield different results to those presented in Chapter 9.

11.3.4.2 Testing interactions between covariates

Interactions between covariates must be examined to ensure that any difference in association between one predictor variable and the outcome at different levels of another predictor variable is taken account of. A description of interactions and how these might impact upon results is described in Chapter 10. Interactions between pain and all covariates are tested by building Cox proportional hazard models using the two variables of interest and an interaction term containing those two variables. If the interaction term has a statistically significant hazard ratio ($p<0.05$), then it must be included in the final Cox proportional hazard model (unless the likelihood ratio test accepts that a smaller model excluding the interaction terms is nested in the bigger model containing the interaction terms).

12.3.4.3 Interpreting Cox proportional hazard output

The hazard ratio output in Stata 14 (Statacorp, 2015) provides a comparison of the hazard of falls in the pain group compared to the non-pain group. If both groups have the same hazard of falling then the hazard ratio would equal 1. A hazard ratio of <1 means that the hazard of falling is less than the control (non-pain) group and a hazard ratio >1 means that the hazard of falling is greater than the control group.

12.3.4.4 Model building for Cox proportional hazards

Univariate analysis is first undertaken within the dataset that is declared as time series. Adopting the same approach as that described in Chapter 10, all covariates are entered into the model in groups using a stepwise approach. Firstly, an unadjusted analysis is undertaken to measure the hazard of falling associated with pain and no other covariates. Covariates are then added to the model in a stepwise manner according to the schedule in Box 10.1, starting with physical health measures (BMI, dizziness, hearing impairment, visual impairment, multimorbidity), then adding mental health factors (anxiety, depression, cognitive impairment), medication factors (total mediation count, maximum analgesic category, NSAID use), physical functioning and previous falls history (baseline self-reported fall).

Statistically significant interaction terms are then added to the most comprehensive model and a likelihood ratio test is conducted to assess whether the interaction terms significantly change the hazard ratios for each covariate.

12.3.4.6 Diagnostic testing of the final model

Cox proportional hazards regression relies on the underlying assumption that the hazard ratio is constant over time and therefore independent of time, for example the risk of falls at two years equals the risk of falls at 4 years. This assumption is tested using Schoenfeld residuals (Schoenfeld, 1982), in which residual values are measured i.e. those values that the model cannot explain). In order for Cox's Proportional Hazard testing to hold, the residual values must be proportional over time. This assumption was tested using generalised linear regression of the scaled Schoenfeld residuals for each variable over time. Where a non-straight line slope indicated a violation of the proportional hazard assumption, time dependent covariates were generated by creating interactions of the predictors and a function of survival time. These were included these in the final model and time varying effects were accommodated using the tvc() option in Stata 14 (Statacorp, 2015). The hazard ratios of time varying covariates are interpreted using the tcv(variable) output.

11.4 Results

781 GP recorded falls and 804 HES recorded falls occurred between the start and end dates of the study period.

11.4.1 Univariate associations between covariates and GP falls

Univariate associations within the dataset are shown in table 11.1. All covariates were statistically significantly related except education status, income adequacy, IMD and NSAIDs.

Table 11.1 Cox proportional hazard ratios for multisite pain and GP-recorded falls: report of statistically significant univariate associations

Covariate	P value
Widespread pain	<0.01
Full time education	0.10
Occupational class	<0.01
Income adequacy	0.20
IMD	0.61
Sex	<0.01
Dizziness	<0.01
Hearing difficulty	<0.01
Vision impairment	<0.01
Maximum analgesic	<0.01
NSAIDs	0.10
Multimorbidity	<0.01
Physical function	<0.01
Baseline self-reported fall	<0.01
Number of pain sites	<0.01
Age	<0.01
Anxiety	<0.01
Depression	<0.01
Cognitive complaint	<0.01
BMI	<0.01
Total medication count	<0.01
IMD = index of multiple deprivation; BMI = body mass index; NSAID = non-steroidal anti-inflammatory	

11.4.2 NPS and GP-recorded falls

Statistically significant interaction terms added to the Cox proportional hazards model were interactions between the number of pain sites and age, cognitive complaint, depression, maximum analgesia, NSAID use and physical functioning.

Table 11.2 presents hazard ratios (HR) and 95% confidence intervals for covariates in each model, from the unadjusted hazard ratio of pain and falls (model 1) through to model 8 (adjusted for all covariates and time-varying covariates); HRs with a p-value of <0.05 are highlighted in bold. The likelihood

ratio test that the small model (contained all the covariates) was nested within the large model (contained all covariates and statistically significant interaction terms) was p=0.40 - therefore the small model was adopted and time-varying covariates were added to this model. Four variables were found to violate the time-constant assumption and were therefore interacted with time (vision, hearing, BMI and maximum analgesic strength).

The number of pain sites was statistically significantly associated with GP-recorded falls until the analysis was adjusted for medication covariates, where the hazard ratio changed from 1.02 ((1.00-1.03) p=<0.01) to 1.01 (1.00-1.02) p=0.08). Model 8 gave the number of pain sites a HR of 1.01 (1.00-1.02) p=0.08.

The final model (model 8) found that increasing age (HR 1.07 (1.06-1.08), p=<0.01), increasing total number of medications (HR 1.05 (1.02-1.08) p=<0.01) and history of self-reported falls at baseline (HR 1.51 (1.22-1.88) p=<0.01) were statistically significantly associated with an increased risk of GP-recorded falls; whilst being male (HR 0.52 (0.44-0.63) p=<0.01) was statistically significantly associated with a reduced risk of GP-recorded falls.

Table 11.2 Hazard ratios (95% CIs and p-values) of a GP recorded fall according to baseline number of pain sites in a multivariate Cox proportional hazard model

Covariate OR (95% CI)	**Model 1 n=11,373**	**Model 2 n=10,254**	**Model 3 n = 9,971**	**Model 4 n = 9,349**	**Model 5 n=9,349**	**Model 6 n=9,234**	**Model 7 n=9,234**	**Model 8 n=9,234**
Number of pain sites	**1.02 (1.02-1.03)**	**1.02 (1.01-1.03)**	**1.02 (1.01-1.03)**	**1.02 (1.00-1.03)**	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Age (years)		**1.08 (1.07-1.09)**	**1.08 (1.07-1.09)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**
Sex: Male		**0.56 (0.47-0.65)**	**0.56 (0.47-0.66)**	**0.51 (0.43-0.62)**	**0.53 (0.44-0.63)**	**0.51 (0.43-0.62)**	**0.52 (0.43-0.63)**	**0.53 (0.44-0.63)**
FT Ed >16y: No		0.92 (0.72-1.17)	0.97 (0.71-1.18)	0.92 (0.71-1.19)	0.91 (0.70-1.17)	0.91 (0.70-1.18)	0.90 (0.70-1.17)	0.90 (0.69-1.16)
Income adequate		0.96 (0.82-1.13)	0.99 (0.84-1.17)	1.00 (0.84-1.18)	1.02 (0.85-1.21)	1.02 (0.85-1.21)	1.02 (0.85-1.21)	1.01 (0.84-1.19)
Occ Class non-manual		1.10 (0.93-1.29)	1.07 (0.90-1.27)	1.09 (0.91-1.30)	1.09 (0.91-1.30)	1.08 (0.91-1.29)	1.08 (0.91-1.29)	1.09 (0.91-1.30)
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 Referent 0.99 (0.78-1.25) 0.81 (0.64-1.04) 0.94 (0.74-1.19) 0.94 (0.74-1.19	 Referent 1.00 (0.79-1.27) 0.79 (0.62-1.02) 0.89 (0.69-1.14) 0.89 (0.70-1.14)	 Referent 1.00 (0.78-1.28) 0.82 (0.63-2.06) 0.89 (0.69-1.16) 0.91 (0.70-1.17)	 Referent 0.99 (0.77-1.28) 0.80 (0.61-1.04) 0.87 (0.67-1.13) 0.88 (0.68-1.14)	 Referent 1.01 (0.78-1.30) 0.81 (0.62-1.05) 0.87 (0.67-1.14) 0.90 (0.69-1.16)	 Referent 1.01 (0.79-1.30) 0.81 (0.62-1.06) 0.87 (0.67-1.14) 0.90 (0.69-1.17)	 Referent 1.01 (0.85-1.30) 0.81 (0.62-1.05) 0.87 (0.67-1.13) 0.90 (0.70-1.17)
Dizzy: Yes			**1.33 (1.12-1.59)**	**1.22 (1.01-1.48)**	1.19 (0.98-1.44)	1.22 (1.00-1.48)	1.19 (0.98-1.45)	1.19 (0.98-1.44)
Hearing deficit: Yes			1.04 (0.86-1.26)	0.99 (0.81-1.21)	0.99 (0.81-.121)	0.98 (0.80-1.20)	0.98 (0.80-1.20)	0.94 (0.88-1.01)
Visual deficit: Yes			1.06 (0.88-1.27)	1.01 (0.83-1.22)	0.99 (0.81-1.20)	0.99 (0.81-1.20)	0.98 (0.81-1.19)	1.02 (0.97-1.08)
CCI score 0 1 2-8			 Referent 1.18 (0.97-1.44) 1.30 (1.02-1.65)	 Referent 1.20 (0.98-1.48) 1.25 (0.97-1.62)	 Referent 1.06 (0.85-1.32) 1.02 (0.77-1.34)	 Referent 1.08 (0.87-1.34) 1.02 (0.77-1.35)	 Referent 1.09 (0.88-1.36) 1.03 (0.78-1.37)	 Referent 1.08 (0.87-1.35) 1.03 (0.78-1.37)
BMI			1.01(0.99-1.02)	1.01(0.99-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.00)

Covariate OR (95% CI)	Model 1 n=11,373	Model 2 n=10,254	Model 3 n = 9,971	Model 4 n = 9,349	Model 5 n=9,349	Model 6 n=9,234	Model 7 n=9,234	Model 8 n=9,234
Depression				1.03 (1.00-1.06)	1.02 (0.95-1.05)	1.02 (0.99-1.06)	1.02 (0.98-1.05)	1.02 (0.99-1.05)
Anxiety				0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.95-1.01)
Cognitive complaint				**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total medication					**1.05 (1.02-1.09)**	**1.05 (1.02-1.08)**	**1.05 (1.02-1.08)**	**1.05 (1.02-1.08)**
Analgesics None Basic Weak op. Mod. op. Strong op.					 Referent 0.91 (0.68-1.22) 0.92 (0.67-1.25) 1.19 (0.89-1.58) 1.19 (0.86-1.65)	 Referent 0.90 (0.67-1.21) 0.89 (0.65-1.23) 1.21 (0.91-1.62) 1.21 (0.87-1.67)	 Referent 0.92 (0.69-1.23) 0.90 (0.65-1.23) 1.20 (0.90-1.61) 1.19 (0.86-1.65)	 Referent 1.02 (0.94-1.11) 0.98 (0.89-1.08) 1.06 (0.97-1.15) 1.03 (0.95-1.14)
NSAIDs: Yes					1.01 (0.78-1.31)	1.04 (0.80-1.35)	1.02 (0.79-1.32)	1.04 (0.80-1.34)
Physical functioning No problem A little A lot						 Referent 1.05 (0.84-1.33) 0.83 (0.62-1.11)	 Referent 1.04 (0.83-1.32) 0.79 (0.59-1.06)	 Referent 1.06 (0.84-1.33) 0.81 (0.60-1.08)
Previous fall: Yes							**1.51 (1.21-1.88)**	**1.51 (1.22-1.88)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; Model 8: Model 7 & adjustment for interaction terms and/or time varying covariates . HR = hazard ratio; 95% CI = 95% confidence interval; where p<0.05, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates and very strong opiates combined. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

11.4.3 Widespread pain and GP-recorded falls

Statistically significant interaction terms included in the analysis were widespread pain and income adequacy, and widespread pain and cognitive complaint.

Table 11.3 presents hazard ratios and 95% confidence intervals for covariates in each model, from the unadjusted hazard ratio of pain and falls (model 1) through to model 8 (adjusted for all covariates and time-varying covariates). Four variables were found to violate the time-constant assumption and were therefore interacted with time (BMI, depression, hearing and analgesia). The likelihood ratio test between the large model (containing the interaction terms) and the smaller model (containing only covariates) found p=0.65, the small model could then be carried forward and time-varying adjusted covariates added accordingly.

'Some pain' was statistically significantly associated with GP-recorded falls at all stages of model building, with the final model giving a hazard ratio of 1.26 ((1.01-1.57) p=0.048)) for 'some pain' compared with no pain. Widespread pain had a statistically significant increased hazard ratio for GP-recorded falls until medication was added to the model. The hazard ratio for widespread pain in the final model (model 8) was 1.27 (0.98-1.65) p=0.07.

Covariates that statistically significantly increased the hazard of GP-recorded falls were increasing age (HR 1.07 (1.05-1.09) p=<0.01), increasing cognitive complaint (HR1.003 (1.00-1.01) p=0.02), increasing number of total medication count (HR 1.05 (1.02-1.08) p=<0.01) and a history of baseline self-reported fall (HR 1.53 (1.23-1.91) p=<0.01). Being male was statistically significantly associated with a lower hazard of falling (HR 0.54 (0.44-0.65) p=<0.01).

Table 11.3 Hazard ratios (95% CIs and p-values) of a GP recorded fall according to pain widespreadness in a multivariate Cox proportional hazard model

Covariate OR (95% CI)	**Model 1 n=11,373**	**Model 2 n=10,254**	**Model 3 n = 9,971**	**Model 4 n = 9,349**	**Model 5 n=9,349**	**Model 6 n=9,234**	**Model 7 n=9,234**	**Model 8 n=9,234**
No pain	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Some pain	**1.37 (1.14-1.65)**	**1.36 (1.12-1.66)**	**1.29 (1.05-1.59)**	**1.32 (1.06-1.63)**	**1.26 (1.00-1.57)**	**1.26 (1.01-1.58)**	**1.25 (1.00-1.57)**	**1.26 (1.01-1.57)**
Widespread	**1.51 (1.24-1.84)**	**1.58 (1.27-1.95)**	**1.41 (1.12-1.76)**	**1.40 (1.10-1.79)**	1.27 (0.99-1.64)	1.26 (0.97-1.64)	1.25 (0.96-1.62)	1.27 (0.98-1.65)
Age (years)		**1.08 (1.07-1.09)**	**1.08 (1.07-1.09)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**
Sex: Male		**0.55 (0.47-0.65)**	**0.56 (0.47-0.66)**	**0.51 (0.43-0.61)**	**0.52 (0.44-0.63)**	**0.51 (0.42-0.61)**	**0.52 (0.43-0.63)**	**0.54 (0.44-0.65)**
FT Ed >16y: No		0.92 (0.72-1.17)	0.91 (0.71-1.17)	0.92 (0.71-1.18)	0.90 (0.70-1.17)	0.90 (0.70-1.17)	0.90 (0.70-1.17)	0.89 (0.69-1.19)
Income adequate		0.94 (0.81-1.11)	0.98 (0.83-1.16)	0.99 (0.83-1.17)	1.01 (0.85-1.20)	1.01 (0.85-1.20)	1.01 (0.85-1.20)	0.99 (0.83-1.18)
Occ Class non-manual		1.11 (0.94-1.31)	1.08 (0.91-1.28)	1.10 (0.92-1.31)	1.10 (0.92-1.31)	1.09 (0.91-1.30)	1.09 (0.91-1.30)	1.09 (0.91-1.30)
IMD								
1)least dep.		Referent	Referent	Referent	Referent	Referent	Referent	Referent
2) 2nd least		0.99 (0.78-1.25)	1.00 (0.79-1.27)	1.00 (0.78-1.28)	1.00 (0.78-1.28)	1.01 (0.79-1.30)	1.02 (0.79-1.31)	1.01 (0.79-1.30)
3)mid dep.		0.82 (0.64-1.04)	0.80 (0.62-1.03)	0.82 (0.63-1.06)	0.80 (0.62-1.04)	0.81 (0.62-1.06)	0.81 (0.62-1.06)	0.81 (0.62-1.06)
4) 2nd most		0.95 (0.75-1.21)	0.89 (0.70-1.14)	0.89 (0.69-1.16)	0.87 (0.67-1.13)	0.88 (0.67-1.14)	0.88 (0.67-1.14)	0.88 (0.67-1.14)
5)most dep.		0.95 (0.75-1.20)	0.90 (0.70-1.15)	0.91 (0.70-1.17)	0.88 (0.68-1.14)	0.90 (0.69-1.17)	0.90 (0.70-1.17)	0.91 (0.70-1.19)
Dizzy: Yes			**1.37 (1.15-1.62)**	**1.24 (1.02-1.50)**	1.20 (0.99-1.45)	**1.23 (1.01-1.49)**	1.20 (0.99-1.46)	1.21 (1.00-1.47)
Hearing deficit: Yes			1.04 (0.86-1.26)	0.98 (0.80-1.20)	0.99 (0.81-1.20)	0.97 (0.79-1.19)	0.97 (0.79-1.19)	0.95 (0.89-1.01)
Visual deficit: Yes			1.07 (0.90-1.29)	1.0 (0.84-1.24)	1.00 (0.82-1.21)	1.00 (0.82-1.22)	0.99 (0.81-1.20)	0.99 (0.82-1.20)
CCI score								
0			Referent	Referent	Referent	Referent	Referent	Referent
1			1.20 (0.98-1.46)	1.21 (0.98-1.48)	1.06 (0.85-1.32)	1.08 (0.87-1.34)	1.09 (0.88-1.36)	1.09 (0.88-1.36)
2-8			1.32 (1.03-1.68)	1.27 (0.98-1.64)	1.02 (0.78-1.35)	1.03 (0.78-1.36)	1.03 (0.78-1.37)	1.04 (0.78-1.38)
BMI			1.00 (0.99-1.02)	1.01 (0.99-1.02)	1.00 (0.98-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.00)

Covariate OR (95% CI)	Model 1 n=11,373	Model 2 n=10,254	Model 3 n = 9,971	Model 4 n = 9,349	Model 5 n=9,349	Model 6 n=9,234	Model 7 n=9,234	Model 8 n=9,234
Depression				1.03 (1.00-1.06)	1.02 (0.99-1.05)	1.02 (0.99-1.06)	1.02 (0.99-1.05)	1.00 (0.99-1.01)
Anxiety				0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.99 (0.97-1.02)
Cognitive complaint				**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	1.00 (1.00-1.01)	**1.00 (1.00-1.01)**
Total medication					**1.06 (1.03-1.09)**	**1.05 (1.02-1.09)**	**1.05 (1.02-1.08)**	**1.05 (1.02-1.08)**
Analgesics None Basic Weak op. Mod. op. Strong op.					 Referent 0.90 (0.67-1.20) 0.90 (0.66-1.24) 1.17 (0.88-1.56) 1.19 (0.87-1.64)	 Referent 0.89 (0.66-1.19) 0.89 (0.64-1.22) 1.20 (0.90-1.60) 1.21 (0.88-1.67)	 Referent 0.90 (0.67-1.21) 0.89 (0.64-1.22) 1.19 (0.89-1.59) 1.19 (0.86-1.65)	 Referent 1.02 (0.94-1.11) 0.97 (0.88-1.07) 1.06 (0.97-1.15) 1.04 (0.95-1.15)
NSAIDs: Yes					1.01 (0.78-1.30)	1.04 (0.80-1.35)	1.02 (0.79-1.32)	1.02 (0.79-1.32)
Physical functioning No problem A little A lot						 Referent 1.05 (0.83-1.32) 0.84 (0.63-1.12)	 Referent 1.04 (0.83-1.31) 0.80 (0.60-1.07)	 Referent 1.09 (0.87-1.37) 0.87 (0.66-1.15)
Previous fall: Yes							**1.51 (1.22-1.88)**	**1.53 (1.23-1.91)**

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; Model 8: Model 7 & adjustment for interaction terms and/or time varying covariates . HR = hazard ratio; 95% CI = 95% confidence interval; where $p<0.05$, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates and very strong opiates combined. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

11.4.4 Univariate associations between covariates and HES falls

Univariate associations within the dataset are shown in table 11.4. Pain measures and socio-economic position indicators (with the exception of IMD) are not statistically significantly associated with HES-recorded falls in univariate analysis. All physical health measures, age, sex, depression, cognitive impairment, total medication count, maximum analgesic category, physical functioning and previous history of self-reported baseline fall are statistically significantly associated with HES-recorded falls in univariate analysis.

Table 11.4 Cox proportional hazard ratios for multisite pain and HES-recorded falls: report of statistically significant univariate associations

Covariate	P value
Widespread pain	0.30
Full time education	0.08
Occupational class	0.06
Income adequacy	0.45
IMD	0.03
Sex	<0.01
Dizziness	<0.01
Hearing impairment	<0.01
Vision impairment	<0.01
Maximum analgesic	<0.01
NSAIDs	0.42
Multimorbidity	<0.01
Physical function	<0.01
Baseline self-reported fall	<0.01
NPS	0.06
Age	<0.01
Anxiety	0.08
Depression	<0.01
Cognitive complaint	<0.01
BMI	<0.01
Total medication count	<0.01
BMI = body mass index, IMD = Index of Multiple Deprivation, NSAIDs = non-steroidal anti-inflammatory drugs	

11.4.5 Number of pain sites and HES-recorded falls

No statistically significant interactions existed when tested. Table 11.5 presents hazard ratios and 95% confidence intervals for covariates in each model, from the unadjusted hazard ratio of pain and falls (model 1) through to model 8 (adjusted for all covariates and time-varying covariates). Anxiety and IMD did not meet the time-constant assumption and were therefore interacted with time.

The number of pain sites had a non-statistically significant relationship with HES falls in univariate analysis, and this moved into a statistically significant relationship when the model was adjusted for demographic factors (HR 1.01 (1.00-1.02) p=0.02); this moved into a non-significant relationship once physical health factors were added to the model (HR 1.01 (0.96-1.02) p=0.25) and the final hazard ratio for HES-recorded falls was 1.00 ((0.99-1.01) p=0.94).

Covariates with a statistically significant hazard ratio for increasing HES-recorded falls are increasing age (HR 1.07 (1.06-1.08) p=<0.01), an increase in total medication count (HR 1.03 (1.00-1.06) p=0.046) and being prescribed strong or very strong opioid medication (HR 1.45 (1.06-1.99) p=0.02).

Being male reduced the hazard of having a HES-recorded fall by almost half compared to being female (HR 0.57 (0.48-0.68) p=<0.01) and a unit increase in BMI was associated with a reduced hazard of HES-recorded falls (HR 0.98 (0.96-1.00) p=0.04).

Table 11.5 Hazard ratios (95% CIs and p-values) of a HES recorded fall according to number of pain sites in a multivariate Cox proportional hazard model

Covariate OR (95% CI)	**Model 1 n=11,373**	**Model 2 n=10,254**	**Model 3 n = 9,971**	**Model 4 n = 9,349**	**Model 5 n=9,349**	**Model 6 n=9,234**	**Model 7 n=9,234**	**Model 8 n=9,234**
Number of pain sites	1.01 (1.00-1.02)	**1.01 (1.00-1.02)**	1.01 (0.96-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Age (years)		**1.08 (1.07-1.09)**	**1.08 (1.07-1.09)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**
Sex: Male		**0.57 (0.49-0.67)**	**0.57 (0.48-0.67)**	**0.56 (0.47-0.67)**	**0.56 (0.47-0.67)**	**0.56 (0.47-0.67)**	**0.56 (0.47-0.67)**	**0.57 (0.48-0.68)**
FT Ed >16y: No		0.97 (0.75-1.26)	0.99 (0.81-1.14)	1.02 (0.77-1.34)	1.01 (0.76-1.32)	1.00 (0.76-1.32)	1.00 (0.76-1.31)	1.01 (0.76-1.33)
Income adequate		1.14 (0.98-1.34)	1.14 (0.97-1.34)	1.13 (0.95-1.34)	1.14 (0.96-1.36)	1.12 (0.94-1.33)	1.12 (0.94-1.33)	1.12 (0.94-1.33)
Occ Class non-manual		0.96 (0.81-1.13)	0.96 (0.81-1.14)	0.99 (0.83-1.18)	0.99 (0.83-1.18)	0.99 (0.83-1.19)	0.99 (0.83-1.18)	0.98 (0.82-1.18)
IMD 1)least dep. 2) 2nd least 3)mid dep. 4) 2nd most 5)most dep.		 Referent 1.05 (0.81-1.35) 1.17 (0.91-1.50) 1.16 (0.90-1.49) 1.21 (0.95-1.56)	 Referent 1.07 (0.83-1.39) 1.16 (0.90-1.49) 1.15 (0.89-1.48) 1.19 (0.92-1.53)	 Referent 1.01 (0.76-1.32) 1.09 (0.84-1.42) 1.06 (0.81-1.39) 1.11 (0.85-1.45)	 Referent 1.02 (0.78-1.33) 1.08 (0.83-1.40) 1.04 (0.80-1.36) 1.09 (0.83-1.42)	 Referent 1.00 (0.76-1.31) 1.07 (0.82-1.40) 1.04 (0.79-1.36) 1.09 (0.83-1.43)	 Referent 1.00 (0.76-1.31) 1.07 (0.82-1.40) 1.04 (0.79-1.36) 1.09 (0.83-1.43)	 Referent 0.99 (0.95-1.04) 1.01 (0.97-1.05) 0.99 (0.94-1.03) 1.00 (0.96-1.05)
Dizzy: Yes			1.17 (0.98-1.39)	1.09 (0.90-1.00)	1.07 (0.88-1.29)	1.07 (0.88-1.30)	1.07 (0.88-1.30)	1.06 (0.87-1.28)
Hearing deficit: Yes			1.01 (0.84-1.22)	1.00 (0.82-1.21)	1.01 (0.83-1.23)	0.99 (0.81-1.21)	0.99 (0.81-1.21)	0.99 (0.81-1.21)
Visual deficit: Yes			1.04 (0.87-1.24)	1.01 (0.84-1.22)	1.00 (0.83-1.21)	0.98 (0.81-1.19)	0.98 (0.80-1.18)	0.98 (0.80-1.18)
CCI score 0 1 2-8			 Referent 1.13 (0.93-1.38) **1.29 (1.02-1.64)**	 Referent 1.07 (0.87-1.32) **1.31 (1.03-1.67)**	 Referent 0.98 (0.78-1.22) 1.13 (0.87-1.47)	 Referent 0.96 (0.77-1.21) 1.16 (0.89-1.51)	 Referent 0.97 (0.77-1.21) 1.17 (0.89-1.52)	 Referent 0.97 (0.78-1.21) 1.17 (0.90-1.52)
BMI			0.99 (0.97-1.01)	0.99 (0.97-1.00)	0.98 (0.97-1.00)	**0.98 (0.96-1.00)**	**0.98 (0.96-1.00)**	**0.98 (0.96-1.00)**

Covariate OR (95% CI)	Model 1 n=11,373	Model 2 n=10,254	Model 3 n = 9,971	Model 4 n = 9,349	Model 5 n=9,349	Model 6 n=9,234	Model 7 n=9,234	Model 8 n=9,234
Depression				1.02 (0.99-1.05)	1.02(0.99-1.05)	1.02 (0.98-1.05)	1.02 (0.98-1.05)	1.01 (0.98-1.04)
Anxiety				0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.95-1.01)	0.98 (0.96-1.01)	1.00 (1.00-1.00)
Cognitive complaint				1.00 (1.00-1.01)	**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total medication					**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**
Analgesics None Basic Weak op. Mod. op. Strong op.					 Referent 1.05 (0.80-1.38) 0.97 (0.72-1.31) 0.87 (0.64-1.20) **1.53 (1.14-2.10)**	 Referent 1.06 (0.80-1.39) 0.92 (0.68-1.26) 0.84 (0.61-1.17) **1.46 (1.07-2.00)**	 Referent 1.06 (0.81-1.40) 0.92 (0.68-1.26) 0.84 (0.61-1.16) **1.46 (1.06-1.99)**	 Referent 1.07 (0.81-1.40) 0.92 (0.68-1.26) 0.84 (0.61-1.16) **1.45 (1.06-1.99)**
NSAIDs: Yes					0.95 (0.73-2.10)	0.92 (0.70-1.21)	0.92 (0.70-1.21)	0.92 (0.70-1.20)
Physical functioning No problem A little A lot						 Referent 1.15 (0.91-1.45) 1.09 (0.82-1.44)	 Referent 1.15 (0.91-1.44) 1.08 (0.81-1.42)	 Referent 1.15 (0.92-1.45) 1.10 (0.83-1.45)
Previous fall: Yes							1.10 (0.88-1.39)	1.11 (0.88-1.39)

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; Model 8: Model 7 & adjustment for interaction terms and/or time varying covariates . HR = hazard ratio; 95% CI = 95% confidence interval; where p<0.05, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates and very strong opiates combined. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

11.4.6 Widespread pain and HES-recorded falls

Statistically significant interaction terms that were added to the Cox proportional hazards model were the widespread pain measure interacted with either pain, IMD, anxiety, total medication count or physical functioning.

Table 11.6 presents hazard ratios and 95% confidence intervals for covariates in each model, from the unadjusted hazard ratio of pain and falls (model 1) through to model 8 (adjusted for time-varying covariate terms). The likelihood ratio test between the model containing all covariates (model 7) and model 7 plus all interaction terms found p=0.21, this meant that the larger model containing the interaction terms was rejected and the time varying covariates were added to model 7; the hazard ratios presented in model 8 (covariates and time-varying covariates, excluding interactions) are therefore be used when interpreting risk associated with HES-recorded falls. One covariate violated the time-constant assumption and was therefore interacted with time (IMD) and this is included in Model 8.

When compared to those with no pain, the 'some pain' group and the 'widespread pain' groups have no statistically significant relationship with HES-recorded falls.

Increasing age (HR 1.07 (1.06-1.08) p=<0.01), an increasing total medication count (HR1.03 (1.00-1.06) p=0.047) and a prescription for strong and very strong opioids (HR 1.47 (1.07-2.01) p=0.02) statistically significantly increased the hazard of HES-recorded falls. Being male (HR 0.56 (0.47-0.67) p=<0.01) and an increase in BMI (HR 0.98 (0.96-1.00) p=0.04) were associated with statistically significantly lower hazards of HES-recorded falls compared to being female and having a lower BMI.

Table 11.6 Hazard ratios (95% CIs and p-values) of a HES recorded fall according to pain widespreadness in a multivariate Cox proportional hazard model

Covariate OR (95% CI)	**Model 1 n=11,373**	**Model 2 n=10,254**	**Model 3 n = 9,971**	**Model 4 n = 9,349**	**Model 5 n=9,349**	**Model 6 n=9,234**	**Model 7 n=9,234**	**Model 8 n=9,234**
No pain	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Some pain	0.96 (0.81-1.13)	0.90 (0.75-1.08)	0.87 (0.72-1.04)	0.86 (0.70-1.04)	0.83 (0.68-1.01)	0.85 (0.69-1.04)	0.85 (0.69-1.04)	0.84 (0.69-1.04)
widespread	1.09 (0.91-1.31)	1.12 (0.91-1.36)	1.04 (0.84-1.29)	1.04 (0.83-1.31)	0.97 (0.77-1.23)	0.99 (0.78-1.26)	0.99 (0.77-1.26)	0.98 (0.77-1.25)
Age (years)		**1.08 (0.91-1.36)**	**1.08 (1.07-1.09)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**
Sex: Male		**0.57 (1.07-1.09)**	**0.56 (0.48-0.67)**	**0.56 (0.47-0.67)**	**0.57 (0.47-0.68)**	**0.56 (0.47-0.67)**	**0.56 (0.47-0.68)**	**0.56 (0.47-0.67)**
FT Ed >16y: No		0.98 (0.76-1.26)	0.99 (0.76-1.29)	1.02 (0.78-1.34)	1.01 (0.77-1.33)	1.00 (0.76-1.32)	1.00 (0.76-1.32)	1.01 (0.77-1.33)
Income adequate		1.13 (0.97-1.33)	1.14 (0.97-1.34)	1.13 (0.95-1.34)	1.15 (0.97-1.37)	1.13 (0.95-1.34)	1.13 (0.95-1.34)	1.12 (0.94-1.34)
Occ Class non-manual		0.96 (0.82-1.14)	0.97 (0.81-1.14)	0.99 (0.83-1.19)	0.99 (0.83-1.18)	0.99 (0.83-1.19)	0.99 (0.83-1.19)	0.98 (0.82-1.17)
IMD								
1)least dep.		Referent	Referent	Referent	Referent	Referent	Referent	Referent
2) 2nd least		1.05 (0.81-1.35)	1.07 (0.82-1.39)	1.00 (0.77-1.32)	1.01 (0.77-1.33)	1.00 (0.76-1.31)	1.00 (0.76-1.31)	0.99 (0.95-1.03)
3)mid dep.		1.18 (0.92-1.51)	1.16 (0.90-1.49)	1.09 (0.84-1.42)	1.01 (0.83-1.40)	1.07 (0.82-1.40)	1.07 (0.82-1.40)	1.01 (0.97-1.05)
4) 2nd most		1.17 (0.91-1.50)	1.15 (0.89-1.49)	1.07 (0.82-1.39)	1.05 (0.80-1.37)	1.04 (0.79-1.36)	1.04 (0.79-1.36)	0.99 (0.94-1.03)
5)most dep.		1.22 (0.95-1.56)	1.19 (0.93-1.54)	1.11 (0.86-1.45)	1.09 (0.83-1.42)	1.09 (0.83-1.43)	1.09 (0.83-1.43)	1.00 (0.96-1.05)
Dizzy: Yes			1.18 (0.99-1.40)	1.09 (0.90-1.32)	1.06 (0.87-1.28)	1.07 (0.88-1.29)	1.06 (0.87-1.29)	1.06 (0.87-1.29)
Hearing deficit: Yes			1.02 (0.85-1.23)	1.00 (0.82-1.21)	1.01 (0.83-1.23)	0.99 (0.81-1.21)	0.99 (0.81-1.21)	0.99 (0.81-1.21)
Visual deficit: Yes			1.04 (0.87-1.24)	1.01 (0.84-1.22)	0.99 (0.82-1.20)	0.98 (0.81-1.18)	0.97 (0.80-1.18)	0.98 (0.81-1.18)
CCI score								
0			Referent	Referent	Referent	Referent	Referent	Referent
1			1.14 (0.94-1.39)	1.07 (0.87-1.32)	0.98 (0.78-1.22)	0.96 (0.77-1.21)	0.97 (0.77-1.21)	0.97 (0.77-1.21)
2-8			**1.30 (1.03-1.64)**	**1.30 (1.02-1.66)**	1.13 (0.87-1.47)	1.15 (0.89-1.50)	1.16 (0.89-1.51)	1.16 (0.89-1.51)
BMI			0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.00)	**0.98 (0.96-1.00)**	**0.98 (0.96-1.00)**	**0.98 (0.96-1.00)**

Covariate OR (95% CI)	**Model 1 n=11,373**	**Model 2 n=10,254**	**Model 3 n = 9,971**	**Model 4 n = 9,349**	**Model 5 n=9,349**	**Model 6 n=9,234**	**Model 7 n=9,234**	**Model 8 n=9,234**
Depression				1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (0.98-1.05)	1.01 (0.98-1.05)	1.01 (0.98-1.05)
Anxiety				0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.96-1.01)
Cognitive complaint				**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	**1.00 (1.00-1.01)**	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total medication					**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**	**1.03 (1.00-1.06)**
Analgesics None Basic Weak op. Mod. op. Strong op.					 Referent 1.07 (0.81-1.40) 0.99 (0.73-1.34) 0.90 (0.65-1.23) **1.57 (1.15-2.13)**	 Referent 1.07 (0.81-1.41) 0.94 (0.09-1.28) 0.86 (0.62-1.19) **1.48 (1.08-2.02)**	 Referent 1.07 (0.82-1.42) 0.93 (0.69-1.27) 0.86 (0.62-1.19) **1.48 (1.07-2.01)**	 Referent 1.07 (0.82-1.42) 0.94 (0.69-1.28) 0.86 (0.62-1.19) **1.47 (1.07-2.01)**
NSAIDs: Yes					0.96 (0.73-1.25)	0.93 (0.71-1.22)	0.93 (0.71-1.22)	0.92 (0.70-1.21)
Physical functioning No problem A little A lot					 Referent	 Referent 1.15 (0.91-1.45) 1.10 (0.83-1.45)	 Referent 1.15 (0.91-1.45) 1.08 (0.82-1.43)	 Referent 1.15 (0.92-1.45) 1.09 (0.83-1.44)
Previous fall: Yes							1.11 (0.88-1.39)	1.11 (0.88-1.39)

Model 1: unadjusted; Model 2: adjustment for demographic covariates; Model 3: Model 2 & adjustment for medical covariates; Model 4: Model 3 & adjustment for mental health covariates; Model 5: Model 4 & adjustment for medication covariates; Model 6: Model 5 & adjustment for physical functioning; Model 7: Model 6 & adjustment for previous falls; Model 8: Model 7 & adjustment for interaction terms and/or time varying covariates . HR = hazard ratio; 95% CI = 95% confidence interval; where p<0.05, this is considered statistically significant and results are highlighted in **bold.** FT Ed >16y = continuing in full time education beyond aged 16 years; IMD= Index of Multiple Deprivation divided into quintiles, where: least dep.= least deprived, 2nd least = 2nd least deprived, mid dep. = middle deprivation category, 2nd most = 2nd most deprived, most dep. = most deprived category. Charlson Comorbidity Index (CCI) score: 0 = no CCI comorbidities, 1 = 1 CCI comorbidity, 2-8 = 2 or more CCI comorbidities. BMI = body mass index. Total medication = total medication count. Analgesics: weak op. = weak opiates, mod. op. = moderate strength opiates, strong op. = strong opiates and very strong opiates combined. NSAID = non steroidal anti=inflammatory drug. Physical functioning = ability to walk 100 yards: no problem = no physical limitation, a little = a little limitation, a lot = a lot of limitation in ability to walk 100 yards. Previous fall = baseline self-reported fall recorded as 'yes'.

11.4.7 Survival analysis: summary

The number of pain sites was not statistically significantly associated with future GP-recorded fall. 'Some pain' was statistically significantly associated with GP-recorded falls, with the final adjusted model finding that those reporting 'some pain' have a 26% increased hazard of a future GP-recorded fall compared to their no pain counterparts (HR 1.26 (1.01-1.57) p=0.048). The presence of widespread pain and future risk of GP-recorded fall almost reached statistical significance, with a HR of 1.27 (0.98-1.65) p=0.07.

Neither the number of pain sites nor widespread pain has a statistically significant relationship with future HES-related falls.

Covariates with a statistically significant relationship to GP and HES-recorded falls are displayed in table 11.7. Of note, history of previous fall was not statistically significantly associated with HES-recorded falls, and physical functioning is not statistically significantly associated with either GP or HES-recorded falls.

Table 11.7 Covariates that have a statistically significant association with GP and / or HES recorded falls in the Cox proportional hazard model after adjustment for all covariates

GP-recorded falls	HES-recorded falls
Covariates increasing the hazard of falling:	
'Some pain' increasing age Increasing cognitive complaint increasing total medication history of self-reported falls at baseline	increasing age increase in total medication count Prescription for strong or very strong opioid medication
Covariates reducing the hazard of falling:	
being male	Being male increase in BMI

11.5 Discussion

11.5.1 Summary of findings

Univariate Cox proportional hazard models found that all covariates except education status, income adequacy, IMD and NSAID use were statistically significantly associated with future risk of GP-recorded falls.

Once the Cox proportional hazard ratio was adjusted for all covariates, including time-varying covariates, the number of pain sites was not statistically significantly associated with future GP-recorded fall (HR 1.01 (1.00-1.02) p=0.08). The measure 'some pain' remained statistically significantly associated with an increased hazard of future GP-fall once all model adjustments had been made (HR 1.26 (1.01-1.57) p=0.048); the increased hazard associated the presence of widespread pain did not quite reach statistical significance (HR 1.27 (0.98-1.65) p=0.07).

Covariates that conferred a statistically significant increased hazard of a GP-recorded fall were increasing age, increasing cognitive complaint, increasing total medication count and history of previous self-reported fall. Being male statistically significantly reduced the hazard of a GP-recorded fall.

Univariate Cox proportional hazard models examining HES-recorded fall found that number of pain sites, the widespread pain measure, education status, income adequacy, NSAID use and anxiety did not statistically significantly predict HES-recorded falls.

The adjusted Cox proportional hazards models containing all covariates, including time-varying covariates, found that only increasing age, increasing medication

count and strong or very strong opioid prescriptions statistically significantly increased the hazard of a HES-recorded fall. Being male and a unit increase in BMI statistically significantly reduced the hazard of falling. The pain measures in these highly adjusted models were not statistically significantly associated with HES-recorded fall (number of pain sites: HR 1.00 (0.99-1.01) p=0.94; widespread pain measure: 'some pain' HR 0.84 (0.69-1.04) p=0.11; 'widespread pain' HR 0.98 (0.77-1.25) p=0.88).

11.5.2 How it fits into the literature and what is new

The results of this chapter are somewhat surprising. The analyses have found that some traditional falls risk factors that are included in falls prevention guidelines do not appear to statistically significantly predict future GP or HES-recorded falls. For example, previous history of fall does not predict HES-recorded falls, limitation in physical functioning and dizziness do not predict either fall-type, and cognitive complaint does not predict HES-recorded falls. This finding is relevant to the (lack of) association between pain measures and GP and HES-recorded falls; possible explanations for the non-prediction of traditional falls risk factors must now be explored to appreciate the relevance to the relationship between pain measures and GP or HES-recorded falls.

The failure of traditional falls risk factors to predict GP or HES-recorded falls may be due to a number of mutually non-exclusive reasons, four of which are summarised below and then discussed in turn:

i) Misclassification of HES and GP fallers due to coding practice and resulting in underestimation of effect estimate;

ii) Risk of bias from measurement of covariates;

iii) Preponderance for falls evidence base and guidelines to be based upon falls outcomes measured using recalled or prospective self-reported falls;

iv) A 'true' result

11.5.2.1 Misclassification of GP and HES fallers

Falls may be under-recorded by GPs. Although there is no firm evidence to support this statement, there are fewer falls recorded in the GP consultation data used in this thesis than in the GP consultation data used by Gribbin et al (2009). Moreover, discussions with local GPs who work in the practices included in the NorStOP cohort unanimously felt that falls are under-coded in GP records. This potential for poor falls coding in GP records may lead to misclassification bias if responders are presenting with fall-related injuries and only the injury is coded, thus meaning the respondent will be classified as a non-faller due to the absence of a falls-code. The same may be true of HES-APC data, as discussed in Chapter 9. This misclassification may lead to lower estimates of falls prevalence and an underestimated effect size. It is therefore possible that some of the traditional falls risk factors, and pain, are not statistically significant predictors of GP and HES-recorded falls simply because their associated hazard is underestimated.

11.5.2.2 Risk of bias from covariate measurement

Three covariates derived from GP records that have been comprehensively collected and reliably measured (age, sex and prescriptions) are the most strongly statistically significantly correlated with future GP and HES-recorded falls. It is therefore possible that it is the measurement and collection of other covariate

information that might be impacting on the lack of relationship between other known falls risk factors and GP or HES-recorded falls.

For example, using baseline self-reported fall as an indicator of previous fall may be problematic. As discussed in Chapter 9, self-reported falls are subject to recall bias leading to misclassification of fallers as non-fallers when respondents fail to recall up to 25% of falls over a three month period (Hannan et al, 2010). Furthermore, the self-reported falls measure only provides a snapshot of the three months prior to survey distribution, thus this may not a long-enough time period for that at risk of falls to sustain a fall and thus become a 'faller'; NICE guidelines recommend ascertaining previous falls history in the past year and use this answer as a basis for falls risk assessment (NICE, 2013).

11.5.2.3 Current evidence base derived predominantly from self-reported falls

Guidelines for falls prevention are developed based primarily upon evidence from studies using self-reported falls as an outcome measure. For example NICE guideline CG161 (NICE, 2013) undertook a systematic review of prospective cohort studies to generate a summary of risk factors for falls in older people. Of the 28 included studies, 20 were based upon self-reported fall outcomes, five were based upon hospital medical records from Finland, Sweden or USA, and three studies did not include details of how the falls outcome was measured. It is therefore not surprising that established risk factors presented in guidelines, for example those by NICE (2013), do not predict GP-recorded or HES-recorded falls in UK data. This thesis has therefore addressed the knowledge gap by providing evidence, in the form of a prospective analysis, of predictive factors for falls that

require GP attendance or hospital admission. Thus, the results of this analysis may simply be reflective of the true population effect estimate.

11.5.2.4 A true result

If the results of the analyses are taken to be reflective of the true population effect estimate for each covariate and its associated hazard of falling, this may suggest that increasing age, sex and BMI are such strong predictors of a fall requiring hospital admission that all other covariate hazard ratios are rendered statistically insignificant. This is biologically plausible since fall-related hospital admissions are often due to associated fragility fractures, which, in turn, are most highly correlated with osteoporosis (for which low BMI, female and older age are risk factors (NICE, 2012)).

Returning to the role of multisite pain as a predictor for GP and HES-recorded falls, the measure of 'some pain' was found to be statistically significantly associated with an increased hazard of a GP-recorded fall. Although this categorisation includes respondents with one pain site, and thus a conclusion cannot be firmly made that multisite pain contributes to GP-recorded fall risk, the majority of respondents in this category (89.1%, n=4665) reported 2 or more pain sites and it is therefore likely that this multisite pain is also associated with an increased hazard of a GP-recorded fall.

11.5.3 Strengths

This analysis is the first to examine to role of multisite pain as a predictor of GP and HES recorded falls. The sample size is large (n=11,375) providing power in analysis to provide effect estimates that are close to the true population effect.

The long duration of follow up (from minimum 3 years to maximum 10 years) is a strength that enables clinically useful recommendations to be given over relevant time frames; as a clinician, it is useful to know what the risk of falling is over the medium and long term is so that preventative strategies that may take some time to be achieved can be put in place to reduce falls risk over a longer time frame.

When appraising the literature to include in their falls prevention guidelines, NICE (2004) described a high quality study as one that did not rely on recall of falls as the outcome measure, a criteria that the analysis in this chapter fulfils, notwithstanding the challenges of falls coding.

As discussed in Chapter 10, the inclusion of multiple covariates enables the analysis to be as reflective of real life clinical practice as possible.

11.5.4 Limitations

The major limitations of this analysis have been discussed above, including the potential bias introduced from poor falls coding and covariate measures.

One further limitation in this analysis is the possible impact of missing data. As the data tables in this chapter show (for example table 11.2), the more covariates added to the model, the fewer respondents are included in analysis. Further interrogation of the data found that, for the covariates with the most missing data, respondents with missing data are generally older. More females had missing physical functioning and cognitive complaint data than males, for example in physical functioning data, 56.6% of the missing-data sample were female compared with 53.7% in the non-missing sample; in the cognitive functioning data 63.1% of the missing-data group were female compared with 53.2% of the non-

missing group. The converse is true for anxiety and depression measures. This pattern of missing data may introduce bias into the analysis; it may be that the missing older people have higher degrees of cognitive complaint and worse physical functioning. Associations between cognitive complaint or physical functioning and falls, or their influence on the relationship between pain and falls may therefore be underestimated since respondents who are more likely to have cognitive complaint or physical limitations are not included in the analysis.

11.5.5 Informing the thesis

The results of this analysis will now be carried forward into Chapter 12, where overall thesis conclusions will be drawn and discussed. This discussion will centre upon the different role that multisite pain appears to have in the prediction of self-reported, GP- and HES-recorded falls and the underlying mechanisms that might be responsible for these relationships.

11.5.6 Chapter summary

This chapter has examined the relationship between baseline pain status and covariate measurements and future GP and HES-recorded falls. The use of survival analysis, specifically using Cox proportional hazard models, has been described and results of univariate and multivariate models were presented. This chapter has addressed the knowledge gap by presenting a prospective analysis of GP and HES-recorded falls within a large sample and the results have been discussed. The final chapter in this thesis will bring together all the results to draw an overall conclusion and put forward recommendations for clinical practice.

Chapter 12: Summary discussion

12.1 Overview

This chapter summarises this thesis' findings, linking them back to the original aims and objectives. Findings that are novel are highlighted, with the potential impact for clinical practice and policy highlighted. Finally, the implications for future research, building on the work from this thesis are presented.

12.2 Summary of findings

This thesis has examined the relationship between multisite pain and falls in older people. The thesis objectives and their associated findings are revisited below:

i) *To describe the prevalence of self-reported falls, falls that require primary health care attendance and falls that require hospital admission in a population-based sample of community-dwelling older people*

Data from a large population cohort found the prevalence to be 12.5% for self-reported falls, 6.9% for GP-recorded falls (falls that result in a utilisation of primary care) and 7.1% for HES-recorded falls (falls that result in utilisation of secondary care).

ii) *To test the hypothesis that older people with multisite pain are more likely to experience a future self-reported fall than older people with no pain*

This thesis found that an increasing number of pain sites were statistically significantly associated with increases odd of a future self-reported fall at three years and six year follow up, even when confounders and putative influencing

variables were accounted for. Each additional pain site conferred a 12% increased odds of falling at three years (OR 1.12 (1.01-1.24) p=0.04) and a 3% increased odds of falling at six years (OR 1.03 (1.02-1.04) p=<0.01). Respondents classified as experiencing 'widespread pain' had 43% greater odds of a self-reported fall than their pain-free counterparts at six years (OR 1.43 (1.06-1.95) p=0.02); the relationship with self-reported falls followed the same pattern but did not reach statistical significance (OR 1.27 (0.92-1.75) p=0.14).

iii) *To test the hypothesis that older people with multisite pain are more likely to seek primary health care for a future fall than older people with no pain*

This study found that the presence of 'some pain' was statistically significantly associated with future falls recorded in GP records compared to those with no pain; this association remained when analysis was adjusted for potential confounders and putative influencing variables. Those reporting 'some pain' (89% of respondents in this group reported two or more pain sites) had a 26% increased risk of falling compared with their pain-free counterparts (HR 1.26 (1.01-1.57) p=0.048). The presence of widespread pain increased the risk of a future GP consultation resulting in a consultation coded as a fall, although the hazard ratio did not reach statistical significance (HR 1.27 (0.98-1.65) p=0.07). The number of pain sites also conferred a small increased risk of future GP-recorded consultation for a fall, although this result was not statistically significant (HR 1.01 (1.00-1.02) p=0.08).

iv) *To test the hypothesis that older people with multisite pain are more likely to be admitted to hospital as a result of a future fall than older people with no pain*

Analysis did not find that multisite pain was associated with an increased risk of future hospital admission for falls (HES-recorded falls) in unadjusted univariate analysis or following adjustment for confounders and putative influencing variables.

12.3 How it fits in with current literature and what is new

The prevalence of self-reported falls within this thesis' study population (12.5%) was lower than current evidence suggests; prevalence estimates from the most comparable study (data from the English Longitudinal Study of Ageing) by Gale et al (2016) found that 28.4% of older people self-reported a fall over the previous two years). The prevalence of self-reported falls in this thesis as measured over a three month recall period is therefore similar, and may be higher than Gale et al's (2016) finding when extrapolated to a two year prevalence. The shorter recall period may therefore increase the accuracy of participant recall, although it does lead to the exclusion of many potential fallers in the analysis.

The increased odds of self-reported falls associated with multisite pain found in this thesis (OR 1.03 (1.02-1.04) p=<0.01 for future six year self-reported fall) do reflect those reported in the meta-analysis of multisite pain and falls presented in Chapter 5 (OR 1.70 (1.49-1.94) for adjusted analysis of prospective cohort studies), albeit to a lesser degree. There is no directly comparable evidence for the prevalence of GP-recorded or HES-recorded falls. As such the data provided

in this thesis is an important additional to the literature, providing evidence from a large population based study on the role of pain on falls risk. The implications of this are discussed below.

12.4 Strengths and weaknesses

This thesis used a large population based sample to examine future falls risk, including 11,375 adults aged 50 years and older who responded to the baseline survey in thesis sample A to examine GP and HES-recorded falls and 4386 participants who completed cohort study follow up (thesis sample B) to assess self-reported falls); thesis sample A is the largest sample size to date in which the relationship between multisite pain and falls is examined.

The demographics of thesis sample A and B are broadly reflective of the local (Staffordshire) and national (UK) populations and thus results are broadly generalisable on a national level. There are however important differences between healthcare service provision in the local area compared to the national picture that may impact upon consultation patterns and thus this thesis' results. For example, North Staffordshire is a relatively under-doctored area compared to other regions so access to primary health care may be more challenging, particularly same-day appointments for acute problems, which may limit the attendance of people with falls unless there is a related problem that they cannot manage at home, for example a more significant injury, in which case it may be that the injury is what is coded as the cause of consultation. Therefore, older people in this thesis' study may not be consulting their GP about falls as often as those living in areas with better access to primary health care.

The selection of covariates to include in analysis was derived from review of the evidence base around falls risk factors, from the systematic review and meta-analysis undertaken to explore to relationship between multisite pain and falls and from clinical experience and discussion with GP colleagues. These complementary approaches are a strength of this thesis' methodology; they enable the inclusion of relevant confounders and putative influencers of the multisite pain-falls relationship to be maximised and therefore mean results are as reflective of real life and daily clinical primary care practice as possible given the choice of variables that were available in the datasets. Despite this rigorous process, there were a few important putative influencers of the pain and falls relationship that would have been preferable to include in analysis if the data were available, for example, fear of falling. If the study were to be repeated, an alternate measure for vision might be used, since the measure used in the thesis specifically excluded the 'need for glasses'. The use of multifocal lens glasses has been found to increase the risk of falls in older people (Lord et al, 2002), it is therefore necessary to include the use of glasses, particularly multifocal lens glasses as a putative influencing factor on the relationship between multisite pain and future falls risk.

The measurements of self-reported, GP and HES-recorded falls are both strengths and limitations of this thesis. For self-reported falls, the reliance on recall may lead to misclassification and underestimates of effect estimates for multisite pain on future falls risk. This risk of underestimation is likely to be consistent across all evidence that uses recall of falls as the measure since the prevalence of self-reported falls in this thesis is likely to be reflective of the current evidence when prevalence over a three month recall period is extrapolated to the two year recall period used by Gale et al (2016) in their UK-based population study of ageing.

The possible increased recall over a shorter duration (three months compared to two years) means that, although the overall prevalence for self-reported falls in the thesis was low, the recall may have been more reflective of the true number of falls sustained during the shorter recall period.

The coding of falls in GP records may not accurately reflect the true prevalence of falls requiring primary health care utilisation for a number of reasons. When a patient presents in general practice, a reason for the consultation is coded as a 'problem title'; this will often reflect the presenting complaint unless a definitive diagnosis can be made. In scenarios where an older person is presenting with an injury due to a fall, it may be that the injury is coded as the 'problem title' and the history of the presenting complaint is documented in free text within the consultation records. For example: *"*Problem title: *pre-tibial laceration* History: *fell yesterday and landed on edge of kerb, sustained cut to shin."* In this example, the READ code for the injury has been entered and a READ code for fall has not been entered. Therefore, data extraction using READ codes to search for fall-related consultations would miss this attendance. Data extraction using a free-text search would be preferable to extract data on fall-related attendances in primary care, although this approach is highly labour-intensive. The discrepancy between the fall-related consultation and the exclusive coding of the presenting complaint is unlikely to be specific to the thesis' dataset. Discussions with GPs working in the local Research Network from which the primary care data is drawn confirmed that falls are not often documented using a READ code during consultations. These GPs have received additional training in the use of READ codes through their employment within the research network. It is therefore possible that, if this is a pattern amongst GPs who have a heightened awareness of the importance and

use of READ codes in research, the discrepancy between fall-related GP consultations and subsequent READ codes is even more common amongst GPs who have not received the additional training. Thus it may be the case that, although the data used in this thesis may underestimate the true prevalence of fall-related GP consultations, it may be more accurate than other primary care datasets which are populated by health care professionals who have not received additional training in consultation READ coding.

Despite the potential underestimation of falls requiring primary health care utilisation, a strength of this thesis is the quality of the GP record data. The information is taken from the Consultations in Primary Care Archive (CiPCA), a dataset that has been previously used for epidemiological research and has been demonstrated to be comparable to national datasets including the General Practice Research Database (now part of the Clinical Practice Research Datalink, the gold standard comprehensive UK dataset for epidemiological research which GP records for 22 million people (CPRD website) (Jordan et al, 2007). The GP practices included in the CiPCA database have been through a robust training programme; this process has been shown to improve data quality and maintain high quality coding standards within the CiPCA practices (Porcheret et al, 2004). Therefore, the data extracted to generate comorbidity scores is likely to be of good quality and reflective of true population prevalences.

In this thesis' dataset, the number of falls requiring hospital inpatient admission coded in HES appears to reflect the number of fall-related injuries requiring hospital admission in HES; the coding of falls is therefore likely to be less of a problem than for falls requiring primary health care utilisation. This difference may be due to the different role of coding in primary and secondary care. For

example, coding is used in secondary care to generate Healthcare Resource Group codes and subsequent payment for services, including falls and any fall-related injury or association (for example, urinary tract infection or fracture). The financial incentive therefore encourages thorough coding and thus HES admitted patient care data is likely to be reflective of the true prevalence of falls requiring hospital admission. In primary care, there is no such system for billing expenses related to falls that required primary care utilisation. Here, the coding is used to build a picture of the patient over time; the records are easy to search and consultations can be read and information easily obtained from the free-text entry; thus there is no strong incentive to code falls in addition to the presenting complaint in the consultation records. The difference in coding practices between primary and secondary health care also may be due to the perceived severity of the fall. For example, a fall that results in a minor soft tissue injury, or a non-injurious fall that occurred as a consequence of a urinary tract infection may not be considered 'severe' and thus is not coded in addition to the presenting complaint in primary care records. Falls that require hospital admission have more immediate, tangible consequences including physical health implications (for example trauma, subsequent pneumonia from hospital admission) and impact on the ability to self-care and live independently; the severity of these consequences may also be driving the coding of falls more accurately within hospital datasets.

The use of the complete dataset in thesis sample B, which consists of respondents who completed six years of cohort study follow up and who consistently completed the pain measures in the questionnaire (the pain screening question for the presence or absence of pain and body manikin), to measure the relationship between multisite pain and future self-reported falls is a strength of the study. This

study population had fewer physical health problems, had fewer medications and strong analgesics prescribed and better physical functioning scores, possibly a consequence of the healthy cohort effect as the more 'unhealthy' baseline respondents dropped out of follow up due to their poor health. This effect may again lead to an underestimation of the true risk that multisite pain contributes to falls within the general population. Using this population adds a novel aspect to the current evidence base; this population were relatively 'healthy' during the cohort study and it is these older adults that will go on to become less healthy over time. Therefore, the study findings relating to future self-reported falls are of particular benefit in primary prevention targeting older adults who have not yet accumulated additional falls risk factors including mulitmorbidity, cognitive impairment and increased medication use, specifically since interventions that may be used to manage pain in older people have the potential to conversely increase the risk of falls in those with complex multimorbidity (for example, analgesia).

As discussed, the number of fall-related codes in HES is similar to the number of fall-related injuries coded in HES, thus only fall-related codes were used to categorise respondents as fallers requiring secondary care admission. The impact of deciding to use only fall-related codes and the possible resulting misclassification bias could be assessed using sensitivity analysis, a technique developed to appraise how study conclusions might be altered by hidden biases, including misclassification bias (Rosenbaum, 2005). Sensitivity analysis would also be useful to further explore the relationship between multisite pain and analgesic use. The univariate analysis in Chapter 8 found that the use of analgesics was statistically significantly associated with an increasing number of pain sites. The multivariate analyses in Chapters 10 and 11, particularly the

relationship between multisite pain categorised into widespread and some pain and both self-reported falls at 6 years and HES-recorded falls, demonstrate a marked change in risk estimate and associated confidence intervals when medication variables are added to the model, more so than with the addition of other covariates. This may be due to the collinearity between the reporting of multisite pain and analgesic use and sensitivity analysis could further test this relationship and thus improve robustness of results.

12.5 How multisite pain acts as a predictor of future falls

Multisite pain is directly associated with an increased odds of self-reported falls, when adjusted for confounders and putative influencers. This means that multisite pain confers additional odds of falling when controlling for other known falls risk factors. Thus improving multisite pain might then lead to a reduction in self-reported falls.

Multisite pain is not directly statistically significantly associated with GP or HES recorded falls. However, the covariates that statistically significantly increase the risk of future GP or HES recorded fall (increasing age, increasing cognitive complaint, increasing total medication count, history of previous fall, being female, strong or very strong opiates) are known, or likely to, be associated with multisite pain (except increasing age). For example, it is known that older adults with multisite pain have poorer health outcomes in general (Lacey et al, 2014), more mobility limitation (Mottram et al, 2008), increasing cognitive complaint (Westoby et al, 2009) and increasing frailty (Wade et al, 2017). In addition, this thesis has found that all covariates were statistically significantly associated with multisite

pain except for increasing age. The influence that multisite pain has upon each of these covariates is biologically plausible and makes clinical sense. For example, multisite pain may be a result of chronic comorbidities that require medication to manage and thus generate a falls risk factor; strong opiates might be prescribed in the management of multisite pain, the side effects of which then lead to future falls; the presence of multisite pain contributes to divided attention and thus impaired ability of those with cognitive impairment to regulate gait steadiness (Sheridan et al, 2003) and therefore increases falls risk. Furthermore the non-association with increasing age reflects the evidence that the number of pain sites is relatively fixed from an early age (Papageorgiou et al, 2002).

These associations with multisite pain mean that the relationship between multisite pain and falls is not simply one whereby reducing the number of pain sites will directly reduce the odds of falling. Multisite pain has a complex relationship with multiple covariates and as such it is the overall burden of multisite pain that is likely to be contributing to self-reported, GP and HES recorded falls; multisite pain is a risk factor for future self-reported falls and a likely influencer of the relationship between other risk factors and future falls.

12.6 Implications for future research and clinical practice

This research has implications for daily clinical practice for GPs and other primary health care professionals. Whilst this research does not establish that reducing the pain will therefore reduce the risk of future falls, it is necessary for older people to be identified so that their other falls risk factors can be addressed. Increased awareness of multisite pain as a risk factor and as a likely influencer of the

relationship between other falls risk factors and falls amongst the general public, GPs and other primary health care professionals will enable older adults with multisite pain to be identified and targeted specifically to reduce their risk of falls.

Increasing awareness that multisite pain is an additional risk factor for falls in older people will be done through publication of this research in peer-reviewed journals. A wider audience will be reached through dissemination of findings in local healthcare bulletins (for example, the Arthritis Research UK Primary Care Musculoskeletal Centre's regular bulletin Musculoskeletal Matters, made available to the general public through display at local GP surgeries), through feedback to the GP practices included in the research and through feedback to the Patient and Public Involvement groups. Findings will also be shared with local GP and primary healthcare professional education groups. This dissemination strategy will increase awareness of the general public and clinicians that multisite pain is a risk factor for falls in older people.

In the context of increasing GP workloads and primary care demand, using an existing framework through which GPs can identify and manage their older patients with multisite pain is more likely to be successful since this will have a relatively small effect on workload compared to undertaking a new initiative. The 2017/2018 GP Contract (the contract of employment between general practices and the UK Government) now includes routine identification of frailty for adults aged 65 years and older, although there are no financial implications for this. In practical terms, this means alerts are placed in the records of all patients aged 65 years and older, which remind the clinician to carry out this assessment. The frailty assessment includes a risk assessment for falls, to be conducted in line with NICE falls prevention guidelines (NICE, 2015; NHS England, 2017) which

emphasis a ‘multifactorial risk assessment and management plan’. An assessment of pain would fit naturally into this framework and, since falls risk assessment is now included in a formal GP Contract, would theoretically be more likely to be carried out. This may not be the case in clinical practice however, since there is no financial reward or penalty attached to the frailty assessment.

In terms of identifying multisite pain as a risk factor for falls, this thesis has provided evidence to be considered in the next update of national guidelines on falls prevention. Using NICE’s (2013) evidence grading system as described in the falls prevention guidelines, this research would be graded as ‘medium’ or ‘high’ due to the large sample, 70% response rate to the baseline questionnaire by respondents, clear methods of measurements of risk factors, adjustment and reporting of all covariates and the use of methods in addition to reliance on recall of fall events (NICE, 2013); it is therefore imperative that this evidence is published in a timely manner.

This thesis has identified that multisite pain is an independent risk factor for self-reported falls, and is likely to be an influencing factor on the pathway between other risk factors and falls and concluded that it is therefore important for clinicians to be identifying their older patients with multisite pain who are at an increased risk of falls and to manage their falls risk accordingly. The next logical question is whether optimally managing multisite pain in older people reduces the risk of future falls. For example, it may be that, although the number of pain sites is relatively stable over the life course, the overall burden of pain may be reduced with interventions aimed at managing pain. General options for managing multisite pain in older people may include patient education and encouragement of self-management, exercise, physiotherapy, analgesics and onwards referral for

conditions likely to benefit from surgical intervention, for example total knee replacements for severe knee osteoarthritis (NICE, 2014). These interventions have the potential to improve physical functioning and general health, reduce comorbidities and their associated medications, reduce the requirement for strong medication and the impact on cognitive functioning and thus reduce the risk of falls. Conversely, it may be the case that, although multisite pain has been identified as a risk factor for self-reported falls in older people and a likely contributor to risk of falls requiring primary and secondary care utilisation, interventions to try and address the pain do not affect the incidence of future falls. In this case, multisite pain may be used as an indicator of falls risk that means individuals require optimisation of other falls risk factors, but that addressing the pain itself is unlikely to reduce future falls risk; of course this is not a reason to sub-optimally manage multisite pain in older people in order to gain other health benefits, for example improved physical functioning and general health.

Thus the next steps are i) to establish whether managing multisite pain in older people reduces the risk of future falls; and ii) to establish what an optimal pain management package might include for older people with multisite pain. A randomised controlled trial is recommended to establish whether managing multisite pain does impact on future falls risk in older people by comparing standard falls prevention assessment and management with standard falls prevention assessment and management and additional identification and management of pain. A pragmatic trial using current standards of care within a community dwelling population who experience multisite pain would yield the most useful clinical information and provide a basis for establishing an optimal pain

management package for older people with multisite pain if the additional pain management in the trial led to reduced future falls risk.

12.7 Conclusion

Falls, whether they are self-reported or result in seeking healthcare, have significant detrimental consequences on individuals, communities and society. This thesis has provided new evidence that multisite pain increases the risk of future falls in older people and it is therefore recommended that older adults with multisite pain are identified in primary care so that appropriate falls prevention assessments and management plans are conducted and future falls are prevented. The evidence presented in this thesis, including the results of the systematic review and meta-analysis, must now be considered for inclusion in national guidelines for the prevention of falls in older people. The next step in the quest to find new interventions to reduce the risk of falls in older people is to establish if managing the multisite pain reduces the risk of future falls in addition to recommended falls prevention programmes.

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Appendix 1: Systematic review and meta-analysis: databases and data sources searched

Platform	Database (dates)
OVID Sp	Medline (1946 to present) Medline in-process and non-indexed Embase (1980 to present) AMED (inception to present) HMIC Health Management Information Consortium: Department of Health, NICE and King's Fund (inception to present) PsychInfo (1806 to present)
NHS Healthcare Databases Advanced Search	BNI (1992 to present) CiNAHL (1981 to present)
Web of Science	the Science Citation Index Expanded (SCI-EXPANDED) (from inception to present) Social Sciences Citation Index (SSCI) (From inception to present) Conference Proceedings Citation Index-Science (CPCI-S) (From inception to present) Conference Proceedings Citation Index-Social Science and Humanities (CPCI-SSH) including conference proceedings of the British Geriatrics Society, The American Geriatrics Society, The Gerontological Society of America and the International Association for the Study of Pain (from inception to present)
Keele University interface	Ageline (inception to present)
Miscellaneous	Cochrane Database of Systematic Reviews (inception to present) Cochrane DARE database (inception to present) TRIP database (inception to present) The Electronic Thesis Online Service (EthOS) (1990 to present)
Charity & Society websites	AgeUK Arthritis Research UK British Geriatrics Society The American Geriatric Society The Gerontological Society of America International Association for the Study of Pain

Appendix 2: Systematic review and meta-analysis: search terminology and example of primary search using more specific terms than ‘pain’ and ‘falls’

MEDLINE	
Pain terms	Exp pain/ Pain.m_titl. (chronic adj3 pain).mp.* (multisite adj3 pain).mp.* (multiple adj3 site anj3 pain).mp.* (multiple adj3 joint$2 adj3 pain).mp.* (multiple adj3 pain).mp.* (multi$ adj3 pain).mp.* Exp musculoskeletal diseases/ Exp musculoskeletal pain/ Musculoskeletal.mp. Exp Osteoarthritis Osteoarthritis.mp. or Osteoarthritis / Osteoarthr$.mp. OA.mp. Arthrosis.mp. (degenerative adj (arthritis or joint or joints)).mp.* Osteoarthritis / or exp osteoarthritis, hip/ or exp osteoarthritis, knee / or exp osteoarthritis, spine/ (hip adj3 (pain or painful)).mp.* (knee adj3 (pain or painful)).mp.* (ankle adj3 (pain or painful)).mp.* (foot adj3 (pain or painful)).mp.* (multi$ adj3 joint$2 adj3 pain).mp. Arthralgia.mp or exp Arthralgia / (arthralgia adj3 (hip or knee or ankle or foot)).mp. *mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier)
Fall terms	Exp Accidental Falls / Accidental fall$.mp. Falls.mp (this term excludes papers relating to the season ‘fall’) Faller$.mp. Falling.mp. Fallen.ti,ab.

Appendix 3: Systematic Review and Meta-analysis: QUIPS assessment for individual domains

1. Study participation							
	a	b	c	d	e	f	Summary
Leveille 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oswald 2006	No	Yes	Yes	Partial	Partial	Partial	Unclear
Furuya 2009	No	partial	Yes	Partial	Yes	Partial	Unclear
Leveille 2009	Yes	Yes	Yes	Yes	Partial	Yes	Yes
Bekibele 2010	yes	partial	Yes	partial	Yes	Yes	Yes
Hayashibara 2010	No	Partial	unsure	partial	yes	yes	Unsure
Holt 2011	No	Partial	unclear	Yes	Yes	Yes	Unclear
Jones 2011	No	Partial	unclear	yes	unclear	yes	Partial
Goes 2012	No	No	no	Partial	Partial	Partial	unclear
Ho 1996	No	No	No	Yes	unclear	no	Unclear
Dore 2015	Partial	yes	yes	Partial	yes	Partial	Partial
Stanmore 2013	no	yes	yes	yes	Unclear	yes	Partial
Patel 2014	Partial	Partial	Partial	yes	yes	yes	yes
Harada 2015	no	Partial	No	Partial	Partial	yes	unclear
Asai 2015	no	no	no	yes	unclear	Partial	unclear
Kitayugachi 2015	no	Partial	yes	yes	unclear	Partial	unclear
Marshall 2016	No	Yes	Yes	yes	unclear	yes	unclear
Stubbs 2015	no	yes	yes	yes	yes	yes	Partial
Kitayuguchi 2016	no	yes	yes	yes	yes	Partial	Unclear

2. **Study Attrition**						
Study	a	b	c	d (i)	d (ii)	Summary
Leveille 2002	Yes	No	Yes	No	Unsure	Unclear
Oswald 2006	Partial	N/A	n/a	n/a	n/a	Partial
Furuya 2009	Yes	No	n/a	n/a	n/a	Unclear
Leveille 2009	Yes	Yes	Partial	No	Unclear	Unclear
Bekibele 2010	Yes	Partial	n/a	n/a	unclear	Unclear
Hayashibara 2010	Yes	partial	partial	No	Unsure	Unsure
Holt 2011	Yes	Yes	n/a	n/a	Unclear	Unclear
Jones 2011	unclear	n/a	n/a	n/a	n/a	Unclear
Goes 2012	unclear	no	n/a	n/a	unclear	Unclear
Ho 1996	unclear	unclear	n/a	n/a	Unclear	Unclear
Dore 2015	unclear	unclear	yes	unclear	Unclear	Unclear
Stanmore 2013	Unclear	no	no	no	unclear	No
Patel 2014	yes	no	n/a	n/a	unclear	Partial
Harada 2015	Partial	no	n/a	n/a	Unclear	unclear
Asai 2015	no	no	n/a	n/a	unclear	unclear
Kitayugachi 2015	No	no	n/a	n/a	unclear	unclear
Marshall 2016	yes	unclear	yes	no	No	Unclear
Stubbs 2015	yes	Partial	n/a	n/a	n/a	unclear
Kitayuguchi 2016	yes	unclear	no	no	unclear	unclear

3. Prognostic factor measurement							
Study	a	b (i)	b (ii)	c	d	e	Summary
Leveille 2002	Yes	Yes	Yes	Yes	Yes	n/a	Yes
Oswald 2006	Yes	yes	Yes	yes	unsure	Unsure	Yes
Furuya 2009	partial	partial	Yes	Unclear	Unclear	Unclear	Partial
Leveille 2009	Yes	Yes	Yes	Yes	Yes	n/a	Yes
Bekibele 2010	Yes	Partial	yes	yes	unclear	n/a	Partial
Hayashibara 2010	Partial	yes	yes	unclear	yes	Unclear	Yes
Holt 2011	Partial	Partial	yes	unclear	unclear	n/a	Partial
Jones 2011	Yes	Yes	Yes	Partial	unclear	n/a	Yes
Goes 2012	Partial	yes	Partial	unclear	unclear	unclear	Partial
Ho 1996	Partial	no	Yes	unclear	unclear	n/a	no
Dore 2015	Partial	Partial	yes	unclear	Partial	n/a	Partial
Stanmore 2013	yes	yes	Partial	yes	yes	unclear	Yes
Patel 2014	Yes	yes	yes	yes	yes	n/a	Partial
Harada 2015	Partial	Partial	yes	yes	unclear	unclear	Partial
Asai 2015	Partial	yes	yes	unclear	unclear	unclear	Partial
Kitayugachi 2015	yes	yes	yes	unclear	unclear	n/a	yes
Marshall 2016	yes	yes	yes	yes	yes	n/a	yes
Stubbs 2015	Partial	Partial	yes	yes	unclear	unclear	Partial
Kitayuguchi 2016	yes	yes	yes	yes	yes	n/a	yes

4. **Outcome measurement**				
Study	a	b	c	Summary
Leveille 2002	No	Partial	Yes	Partial
Oswald 2006	No	partial	Unsure	Partial
Furuya 2009	No	Partial	Unsure	Partial
Leveille 2009	Yes	Yes	Yes	Yes
Bekibele 2010	No	Partial	Yes	Partial
Hayashibara 2010	Yes	Yes	Unclear	Yes
Holt 2011	No	Partial	Unclear	Partial
Jones 2011	Yes	Partial	Yes	Partial
Goes 2012	Yes	Partial	unclear	Partial
Ho 1996	Partial	Partial	Unclear	Partial
Dore 2015	no	Partial	yes	Partial
Stanmore 2013	yes	yes	yes	Yes
Patel 2014	yes	Partial	yes	Partial
Harada 2015	no	no	yes	Partial
Asai 2015	no	Partial	unclear	Partial
Kitayugachi 2015	yes	Partial	unclear	Partial
Marshall 2016	Partial	Partial	yes	Partial
Stubbs 2015	yes	Partial	yes	Partial
Kitayuguchi 2016	Partial	Partial	yes	Partial

5. Confounding								
Study	a	b	c	d	e	F (i)	F (ii)	Summary
Leveille 2002	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Partial
Oswald 2006	Partial	Partial	Partial	Unsure	Unclear	N/A	Partial	Partial
Furuya 2009	partial	no	Partial	unsure	Unsure	n/a	Partial	Partial
Leveille 2009	Yes	Yes	Partial	Yes	n/a	Partial	Yes	Yes
Bekibele 2010	Partial	Partial	Partial	Unsure	Unsure	Partial	Yes	Yes
Hayashibara 2010	Yes	Partial	Unclear	Unclear	n/a	n/a	Yes	Partial
Holt 2011	Partial	Partial	Partial	unclear	unclear	unclear	No	No
Jones 2011	Partial	yes	Partial	unclear	unclear	no	no	No
Goes 2012	No	Partial	Partial	unclear	unclear	Partial	Partial	Partial
Ho 1996	Partial	Partial	Partial	unclear	unclear	Partial	Partial	Partial
Dore 2015	yes	unclear	unclear	yes	unclear	Partial	yes	Partial
Stanmore 2013	yes	yes	yes	yes	unclear	no	yes	Partial
Patel 2014	yes	yes	Partial	yes	unclear	no	yes	Partial
Harada 2015	Partial	yes	Partial	yes	unclear	No	Yes	No
Asai 2015	Partial	Partial	Partial	unclear	unclear	n/a	Partial	Partial
Kitayugachi 2015	Partial	Partial	Unclear	unclear	n/a	n/a	Partial	Partial
Marshall 2016	Partial	yes	Partial	yes	n/a	n/a	Partial	Partial
Stubbs 2015	Partial	yes	Partial	yes	n/a	n/a	yes	Partial
Kitayuguchi 2016	Partial	Partial	Partial	yes	yes	n/a	Partial	Partial

6. Statistical analysis reporting					
Study	a	B (i)	B (ii)	c	Summary
Leveille 2002	Yes	Partial	Yes	Yes	Yes
Oswald 2006	Yes	yes	yes	yes	Yes
Furuya 2009	Partial	Yes	Yes	Yes	Partial
Leveille 2009	Yes	Yes	Yes	Yes	Yes
Bekibele 2010	yes	yes	yes	Partial	Partial
Hayashibara 2010	Yes	Yes	Yes	Yes	Yes
Holt 2011	Partial	n/a	n/a	Yes	Partial
Jones 2011	Partial	n/a	n/a	Yes	Partial
Goes 2012	yes	yes	yes	yes	yes
Ho 1996	Partial	Partial	Partial	unclear	Partial
Dore 2015	yes	Partial	yes	yes	yes
Stanmore 2013	yes	yes	yes	yes	yes
Patel 2014	yes	yes	yes	yes	yes
Harada 2015	yes	yes	yes	yes	yes
Asai 2015	yes	Partial	yes	yes	yes
Kitayugachi 2015	yes	yes	Partial	yes	Partial
Marshall 2016	Partial	Partial	Partial	Partial	Partial
Stubbs 2015	yes	Partial	yes	unclear	Partial
Kitayuguchi 2016	yes	yes	Partial	yes	Partial

Appendix 4: Multisite pain and falls: Systematic review and Meta-analysis

Table containing all extracted results from the twenty studies included in the systematic review

Author	Outcome measure method	No pain group / comparison group description	Single site pain & risk of falls (OR with 95% CI) unless otherwise specified	Multisite pain & risk of falls (OR with 95% CI) unless otherwise specified	Risk of bias (high/ low/ unclear)
Ho 1996	Face-to-face interviews	No pain reported in interview	Lower limb joint pain in left or right limb: 1.2 (0.8-1.8) Adjusted (age and sex)	Bilateral lower limb joint pain: 1.4 (1.1-1.8) Adjusted (age and sex) Bilateral wrist pain: 1.28 (1.13-1.44) Unadjusted*	High
Leveille 2002	In-home interviews	No pain or only mild pain (score <4 on numerical rating scale) reported in interview	No pain or mild pain one site is the referent group	1 + falls: Moderate / severe pain lower extremities OR 1.27 (0.97-1.66) Widespread pain OR 1.66 (1.25-2.21) Recurrent falls: Moderate / severe pain lower extremities OR 1.38 (0.93-2.03) Widespread pain OR 1.66 (1.10-2.50) All adjusted (age, race education, BMI, confirmed diseases (hip fracture, angina pectoris, diabetes mellitus, peripheral arterial disease, stroke, Parkinson's disease), walking disability, previous fall in 12 months before baseline, MMSE score, daily use of psychoactive medications, daily	Medium

				use of analgesic medications, gait speed, balance test score, proxy respondent and follow-up round)	
Oswald 2006	Self-completed survey	Number of tender joints during clinical examination and indicated on mannequin	Hip tenderness: no association Ankle tenderness: no association Foot tenderness: no association Knee tenderness: 1.09 (1.1-2.1) Adjusted for age Knee deformity: 2.1 (1.0-4.4) Adjusted for age	1.2 (0.9-1.6) Per 10 count increase in joint tenderness Adjusted for age	High
Furuya 2009	Self-completed survey	Number of tender joints reported during clinical examination and self-reported survey	Unable to extract this information	1.39 (1.14-1.70) Per tender joint count increase Adjusted (age, sex, BMI, disease duration, J-HAQ score, ESR, CRP, DAS-28. VAS pain, VAS general health, swollen joint count, TKR or THR, NSAID use, prednisolone dose, methortrexate use, any osteoporosis drug use, active vitamin D3 use, bisphosponate use)	High
Leveille 2009	Daily completion of monthly falls postcards	No pain reported during interview	% participants fall in past year No pain = 28.3% Polyarticular pain = 38.3% Single site rate ratios (no pain referent group): 1.19 (0.90-1.56) adjusted for socioeconomic characteristics (Model 1) 1.15 (0.86-1.53) adjusted for Model 1 plus chronic conditions, physical and cognitive status	Polyarticular pain = 44.2% P <0.001 across groups no pain/ single site pain / multisite pain Multisite pain rate ratios (no pain referent group) 1.70 (1.34-2.16) adjusted for socioeconomic characteristics (Model 1) 1.71 (1.33-2.20) adjusted for Model 1 plus chronic conditions, physical and cognitive status (Model 2)	Low

			(Model 2) 1.11 (8.84-1.47) adjusted for Model 2 plus physical performance and psychotherapeutic medications (Model 3) 1.11 (0.84 – 1.48) adjusted for Model 3 plus analgesic use and hand and knee arthritis clinical criteria	1.60 (1.23-2.06) adjusted for Model 2 plus physical performance and psychotherapeutic medications (Model 3) 1.53 (1.17-1.99) adjusted for Model 3 plus analgesic use and hand and knee arthritis clinical criteria	
Bekibele 2010	Interviews	No pain reported during interview	1.0 (0.6-1.5) Adjusted (age and sex)	1.2 (1.0-1.4) Adjusted (age and sex)	Medium
Hayashibara 2010	Daily completion of monthly falls calendars	No tender joints reported during clinical examination	Not possible to extract this information	Mean tender joint count in fall group: 4.30 (SD 7.02) Mean tender joint count in no-fall group: 3.18 (SD 4.88) p = 0.41 No significant difference in the mean tender joint count between fall group and no-fall group	Low
Holt 2011	Structured interview	Absence of neck and back pain	2.42 (0.87-6.71) Unadjusted	0.80 (0.29-2.19) Unadjusted	High
Jones 2011	Self-completed form	Number of painful body regions recorded in self-reported survey in healthy control group	Not possible to extract this information	5.31 (1.63-17.26)	High
Goes 2012[appendix]	Interview	Physician-assessed tender points in lower limbs and general pain in healthy	Not possible to extract this information	5.44 (0.91 – 32.31)	High

		control group			
Dore 2015	Unclear: participants underwent intial home interview, a clinic visit and a second home visit	Symptomatic OA in hips or knees (presence of pain, aching and stiffness on most days associated with radiographic changes). Groups are no symptomatic OA, mild symptoms and moderate / severe symptoms. Author grouped into no pain, pain in either joint, pain in both joints	Unable to compare no pain with pain as it is not clear that those grouped as no hip pain also had no knee pain.	1 symptomatic joint OR 1.53 (1.10-2.14) 2 symptomatic joints OR 1.74 (1.19-2.53) 3-4 symptomatic joints OR 1.85 (0.96-3.55)	Medium
Stanmore 2013	Prospective daily falls calendars and monthly telephone call where necessary.	Number of swollen or tender joints and presence or absence of joint tenderness	Unable to calculate this information	Unadjusted bivariate LR compared to no swollen / tender joints: LR 1.0 (0.98-1.04). Presence of lower extremity joint tenderness /swelling: OR 2.0 (1.3-2.8) unadjusted Presence of lower extremity joint tenderness / swelling : 1.7 (1.1-2.8) $p<0.05$ adjusted for 16 predictive risk factors (Swollen or tender lower extremity joints, DAS28 score, use of psychotrophic medications, taking 4 or more types of medications, taking steroids at baseline, VAS pain score, VAS fatigue score, 12 month history of single fall, 12 month history of multiple falls, history of fracture, history of injuries from previous falls, short FES-I score, HAQ score, Four-Test Balance	Low

				Scale, Symsptoms of feeling dizzy or unsteady, time taken to complete the Chair Stand Test) Presence of lower extremity joint tenderness / swelling OR 1.7 (1.1-2.7) p<0.05 adjusted for 12 explanatory risk factors (Swollen or tender lower extremity joints, DAS28 score, use of psychotrophic medications, taking 4 or more types of medications, taking steroids at baseline, VAS pain score, VAS fatigue score, short FES-I score, HAQ score, Four-Test Balance Scale, Symptoms of feeling dizzy or unsteady, time taken to complete the Chair Stand Test)	
Patel 2014	Interviewer question	Total number of pain sites, no pain is referent group. Number of pain sites 0, 1,2,3 or 4.	Unable to calculate this information	Prevalence ratio for fall yes/no and pain, no pain is referent group: NPS 1 1.21 (1/06-1.38) NPS 2 1.53 (1.31-1.79) NPS3 1.54 (1.30-1.83) NPS4 1.75 (1.51-2.04) All adjusted for age, sex, ethnicity, education, smoking, BMI, depressive symptoms, obesity, dementia, arthritis, OP, hip fracture, chronic lung disease, MI, DM, hypertension, stroke, number of medical conditions, coginitive performance, exercise, frequency analgesic use, chair rise performance, gait speed, grip strength, standing balance performance	Low
Harada 2015	Postal questionnai	Knee pain or low back pain	Risk of falls with one pain site OR 1.40 (0.97-2.03) unadjusted,	Risk of falls with two pain sites OR 2.19 (1.53-3.12) p<0.001 unadjusted,	High

	re	experienced in the last month yes/no	OR 1.42 (0.98-2.06) adjusted for age and sex, OR 1.37 (0.95-2.00) adjusted for multiple variables**	OR 2.19 (1.53-3.12) p<0.001 adjusted for age and sex, OR 1.93 (1.35-2.78) p<0.001 adjusted for multiple variables**	
Asia 2015	questionnaire (no further information)	Pain in the back, hip, knee, foot or toe lasting 1 month or more in the previous year and also present in the previous month. Number of pain sites were counted and grouped into no pain, single-site pain and 2 or more pain sites	The OR is presented using number of chronic MSK pain sites as a continuous variable:	OR 5.02 (1.50-17.88) p=0.03 unadjusted OR 5.31 (1.40-21.50) p=0.03 adjusted for physical function and fear of falls i.e. the odds of falling increases by 5.02 for each additional site of pain	High
Kitayuguchi 2015	Self-administered survey and face-to-face interview	LBP and knee pain 'how much pain have you had during the last week? None, mild, severe, very severe. None is no pain group, mild – very severe is pain group	For single falls: Knee pain only: OR 0.83 (0.28-2.50) adjusted for age, sex, BMI; OR 0.71 (0.23-2.21) adjusted for all*** LBP only: 1.56 (0.66-3.65) adjusted for age, sex, BMI; OR 1.27 (0.52-3.07) adjusted for all *** For multiple falls: Knee pain only: OR 3.58 (0.32-40.48) adjusted for age, sex, BMI; OR 3.34 (0.29-85.83) adjusted for all***	For single falls: Knee and LBP OR 2.16 (1.02-4.57) p<0.05) adjusted for age, sex, BMI; OR 1.50 (0.67-3.39) adjusted for all*** For multiple falls: Knee pain and LBP OR 11.07 (1.43-85.83) < 0.05 adjusted for age, sex, BMI; OR 10.79 (1.33-87.19) p<0.05 adjusted for all***	High

			LBP only: OR 2.69 (0.24-30.39) adjusted for age, sex, BMI; OR 2.49 (0.22-28.52) adjusted for all***		
Stubbs 2015	Interviewer administered questionnaire	Chronic MSK pain defined as report of MSK pain present over the past month and for at least 3 months of the previous year. Then classified into no CMP, single site CMP and multisite CMP (pain at 2+ sites)	Any fall: OR 1.83 (0.97-3.43) adjustment 1 (adjusted for age and sex); OR 1.50 (0.72-3.13) adjustment 2****; OR 1.18 (0.56-2.56) adjustment 3**** Single fall: OR 1.34 (0.67-2.65) adjustment 1, OR 1.21 (0.54-2.69) adjustment 2, OR 1.05 (0.46-2.39) adjustment 3. Recurrent falls: OR 1.97 (0.85-4.56) adjustment 1, OR 1.64 (0.62-4.32) adjustment 2, OR 1.40 (0.51-3.78) adjustment 3.	Any fall: OR 3.53 (1.97-6.34) p<0.05 adjustment 1, OR 2.36 (1.15-4.85) p<0.05 adjustment 2, OR 1.92 (0.89-4.13) adjustment 3. Single fall: OR 1.39 (0.74-2.59) adjustment 1, OR 0.98 (0.44-2.10) adjustment 2, OR 0.78 (0.33-1.81) adjustment 3. Recurrent falls: OR 4.22 (2.08-8.56) adjustment 1, OR 3.56 (1.46-8.67) adjustment 2, OR 3.43 (1.34-8.65) adjustment 3.	Medium
Marshall 2016 ****** (see results table for more results not strictly relating to SSP and MSP and falls)	Survey administered in clinic	Any back pain in the last 12 months? Yes / No. Those reporting yes indicated on a drawing where their pain usually occurred – upper, middle or lower back. Classified into no pain, lower only, middle only, upper only. Also number of pain sites as 0,1,2,3. Hip pain yes/ no	Back pain single site and any fall: RR 1.26 adjusted for age RR 1.12 (1.10-1.33) adjustment 2 Back pain single site and 2+ falls: RR 1.58 adjusted for age RR 1.49 (1.12-1.78) adjustment 2	Back pain 2 sites and any falls: RR 1.34, adjusted for age RR 1.27 (1.12-1.44) adjustment 2 Back pain 2 sites 2+ falls: RR 1.73 RR 1.63 (1.30-2.05) adjustment 2 Back pain 3 sites and any falls: RR 1.60 adjusted for age RR 1.50 (1.23-1.83) adjustment 2 Back pain 3 sites and 2 + falls RR 1.60 RR 1.50 (1.23-1.83) adjustment 2	Medium

Kitayuguchi 2016 *******	Postal questionnaire	Presence or absence of knee pain of LBP on day of survey, classified into pain lasting > 3 months, pain < 3 months or no pain. Multisite classified as no chronic LB or KP, either chronic LBP or knee pain and both chronic LBP and KP.	Chronicity and 1+ falls: Either LBP or KP: OR 1.51 (1.01-2.27) unadjusted, OR 1.35 (0.87-2.09) adjusted Intensity and 1+ falls: Either moderate / severe LBP or KP: OR 1.57 (1.10-2.26) OR 1.40 (0.94-2.10) Chronicity and 2+ falls: Either chronic LBP or KP: OR 1.59 (0.88-2.89) OR 2.12 (0.67-6.74) adjusted Intensity and 2+ falls: Either chronic LBP and KP: OR 1.50 (0.83-2.71) OR 1.17 (0.63-2.20) adjusted	Chronicity and 1+ falls: Both chronic LBP and KP: OR 2.42 (1.29-4.54) OR 2.03 (0.95-4.33) adjusted Intensity and 1+ falls: Both chronic LBP and KP: OR 2.99 (1.13-3.53) OR 1.57 (0.80-3.05) adjusted Chronicity and 2+ falls: OR 1.59 (0.88-2.89) OR 2.12 (0.67-6.74) adjusted Intensity and 2+ falls: OR 2.55 (1.18-5.53) OR 1.58 (0.60-4.17)	Medium
Brenton-Rule 2016	Survey at a baseline visit	Tender joint count	Unable to calculate this information	Tender joint count lower limb (mean, SD): Non-fallers 4.98 (6.9) Fallers 6.63 (7.37) P = 0.04	Medium

*classed as unadjusted as not clear from manuscript (manuscript explicitly states OR that are adjusted); BMI = body mass index; MMSE = Mini-Mental State Examination; J-HAQ = Japanese Health Assessment Questionnaire; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS-28 = Disease activity score; VAS = Visual analogue scale; TKR = total knee replacement; THP = total hip replacement; NSAID = Non-steroidal anti-inflammatory drug; **Harada 2015 – multiple variable included in adjustment were age, sex, lower limb functional decline; *** Kitayuguchi 2015 – adjusted for age, sex, BMI, self-rated health, self-reported psychological distress, medication number, gait speed, exercise time; ****Stubbs 2015 – adjustment 2 for age, sex, number of chronic conditions, number of prescribed medications, HRQoL and TUG; ***** Stubbs 2015 – adjustment3 for adjustment 2 + physical activity and fear of falling; ******Marshall 2016 – adjustment 2 is adjusted for age, education, smoking, alcohol, self-rated health, history of physician diagnosed conditions including Parkinson's Disease, stroke, and OA. Past 12 month history of falls, fainting, hip pain. ADK score, depression, medication use in past 12m , medications for sleep, anxiety, pain. Physical performance measures, BMI, presence of vertebral fracture; ******* Kitayugachi 2016 – adjusted for adjusted for age, sex, BMI, community, education years, self-rated health, depression, smoking, chronic disease history, medication use, consultation with physician; Dore 2015 adjusted for ethnicity, sex, age, BMI, falls at baseline, lung problems, neurological problems, narcotic use

Appendix 5: Ethical and legal aspects of using participant identifiable data for secondary data analysis without explicit consent

Introduction

This section details the processes involved in preparing applications for the National Information Governance Board under Section 251 of the NHS Act 2006. The literature review and Patient and Public Involvement exercise that informed the subsequent applications required for data linkage are described. The outcome of the application process is presented and a chapter summary is provided.

Overview

In order to address this theses' objectives, the NorStOP survey data, GP consultation records, prescription records, HES and ONS data need to be linked, a process is undertaken by the NHSIC using identifiable data sent by this thesis's research team. In research, the use of identifiable data generally requires the consent of the study participant, which this thesis's author did not have thus giving rise to a challenging situation. A thorough understanding of the ethical and legal aspects was therefore imperative to proceed correctly with the proposed research, starting with the basic concepts of confidentiality and consent in research. These concepts are now discussed and the law governing a researcher's duty of confidentiality is outlined and applied to the proposed research to define the specific ethical challenges. Mechanisms to overcome the ethical challenges are then presented. Finally, a literature review and description of PPI involvement are described and then used to justify the decisions made during the data acquisition

process in order to obtain permission to undertake data linkage. Note that this work was undertaken and completed in 2012; the National Information Governance Board who oversaw the process of acquiring data ceased to function in May 2013 and its function has been transferred to the National Information Governance Committee

The ethical principles of research: confidentiality and consent

Researchers have a moral duty to conduct ethically-sound research. Guidance has been produced to assist researchers in achieving good ethical standards in their research. In the UK, guidance from the National Institute of Health Research (NIHR) states 'clinical studies should be carried out according to the International Conference on Harmonisation and the World Health Organisation Good Clinical Practice standards' (NIHR, 2011). This guidance is drawn from the Declaration of Helsinki, which states:

> *'it is the duty of physicians [and others] who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimise the impact of the study on their physical, mental and social integrity'.* (WMA 2008)

A priority for researchers is therefore to design and conduct research that protects participants' right to confidentiality.

In the UK, an individual's right to confidentiality is protected by the Human Rights Act 1998, The Data Protection Act 1998 and the English Common Law Duty of

Confidentiality. The Human Rights Act 1998, Article 8 states that individuals have a right to private and family life including the right to have one's medical information kept private and confidential (Department for Constitutional Affairs, 2006). The Data Protection Act 1998 regulates the use of personal information by organisations and individuals, including healthcare professionals and researchers, thus ensuring such information is kept private and confidential (Information Commissioner's Office 2012). The Common Law holds a general position that if information is given in circumstances where a duty of confidence is expected, that information cannot normally be disclosed without the information provider's consent (DoH 2008). Applying this to medical research, this means that patient information must not normally be disclosed without the consent of the patient (or research participant) (DoH 2008). Therefore, seeking consent is a means of protecting patients' and research participants' rights to confidentiality. Indeed, the NIHR's Good Clinical Practice states 'informed, voluntary consent to participate in research is a fundamental principle of ethical research practice' (NIHR 2011). Respecting an individual's right to dissent from research is therefore equally important in research practice.

6.3.2 The context of identifiable, sensitive patient information

Under the duty of confidentiality, the type of patient information used in the research is a key consideration. Although the duty of confidentiality covers all aspects of an individual's health and social care information, information required by researchers that is deemed 'identifiable' or 'sensitive' is of particular interest. *Patient identifiable information* is defined by the Department of Health (2003) as 'any information that may be used to identify a patient directly or indirectly'. Direct identifiers include name, address, full postcode, date of birth, NHS number and

date of death (NHSIC 2012a). Information can also be linked together to identify patients, for example a rare disease in a specific geographical area or a small population. *Sensitive information* is defined by the Hospital Episode Statistics department (2012b) as information relating to the medical practitioners treating the patient and information about the patient's legal status under Mental Health legislation. In addition, the NHS Health and Social Care Information Centre (2012a) also include racial or ethnic origin and physical or mental health conditions as sensitive information.

6.3.3 Defining the challenges of this thesis' proposed research

The proposed research involves linking participants' pre-existing survey data with their medical records and national (HES and ONS) datasets. The dataset used for analysis will therefore contain linked survey responses and health care records for each individual participant. Obtaining consent from participants to partake in research is required to ensure sound ethical research practice. The challenge specific to the proposed research in this thesis is now dicussed.

Consent to participate in research was obtained during baseline and follow-up NorStOP surveys, as approved by the Local Research Ethics Committee (05/Q2604/20 NorStOP 1, 05/Q260472 NorStOP 2 and 06/Q2801/90 NorStOP 3). Consent to link survey responses to '*medical records'* was requested in the NorStOP baseline surveys and was given by 75% of respondents. Specifically, consent was sought through the following paragraph:

"it is important for us to find out what types of treatment and tests people need. We can do this by reviewing medical records. Would you be willing to give your permission for this? When we review the medical records, your name will not be used so that you will not be identified personally. We can assure you that any

information will be held in the strictest confidence." (NorStOP 1 baseline General Health Questionnaire)

4666 NorStOP participants therefore refused consent to access and link medical records with their survey data.

It was not possible to obtain consent from NorStOP participants to access their HES and ONS information and link it with their survey responses for a number of reasons. Firstly, the NorStOP surveys began recruiting in 2002. The recorded contact details of participants are were more than ten years old in some case which meant those participants would be very difficult to trace. Secondly, it was possible that some participants had died, particularly given that the cohort compromised of older adults. Therefore, it was considered that sending study correspondence to deceased participants or their surviving relatives was not in the best interests of the surviving relatives. Finally, attempting to trace 18,497 NorStOP baseline respondents who may have moved out of the area or died would have been an expensive process in terms of time, personnel and bureaucracy. Thus, the situation of consent for the proposed research is challenging, since it was not possible to obtain participant consent for access to, and linkage of, HES and ONS data.

This situation gives rise to two requirements:

i) *A mechanism that enables HES and ONS access and data-linkage despite the inability to obtain consent*
ii) *An assessment of the wishes of those who dissented from medical record review with respect to accessing HES and ONS data*

The following sections discuss address these important questions.

6.3.4 A mechanism to enable HES and ONS data access and linkage despite no participant consent: the NHS Act 2006, section 251

The first step towards finding a solution was to consider how the HES and ONS data is accessed and linked to the NorStOP participants. The data was accessed and linked by the NHSIC. The NHSIC required specific information about the NorStOP participants to allow the correct HES and ONS data to be extracted and linked. The research team needed to provide the IC with individual identifiers including NHS number, post code, date of birth and sex; the pseudo-anonymised study number was also be provided for each participant. The IC returned a dataset of ONS and HES data that is linked to each participant's individual study number, thus the data was retuned in a pseudo-anonymised format. 'Pseudo-anonymised' describes a process whereby specific patient identifiers are replaced by alternative (and otherwise meaningless) alphanumeric fields (Care Record Development Group 2007).

NHS number and post code were not held by the NorStOP Data Custodian (the person responsible for the 'safekeeping of data and control of their use, and eventual disposal, all in accordance with legislation and terms of consent provided by the data-provider [i.e. patient]'), (Medical Research Council 2012). Therefore, in order to obtain the identifiable data to send to the IC, the Data Custodian had to request the identifiable information from the primary key holder (the GP practices from which the NorStOP samples were drawn). Once the data linkage had been achieved in the Research Centre, identifiable data including NHS number and post

code were deleted. Ethical permission was already in place to store date of birth and sex in the NorStOP database and these fields will be used in data analysis.

Thus, to enable access to the HES and ONS data, two specific data-handling processes had to be undertaken, both of which required the use of identifiable data:

i) The research team had to liaise with the participant's GP surgery in order to obtain the NHS number and post code for participants through secure encrypted pathways. The study team held the pseudo-anonymous practice identifier for individuals in the cohort. This is the primary key which enabled the GP surgery to establish a link back to participants' identifiable data which was securely held in the surgery; and

ii) The research team to send NHS number, postcode, DOB and sex to the NHSIC through secure encrypted pathways to enable data-linkage with HES and ONS data.

The HES and ONS data will include information about physical and mental health which is classified as sensitive data.

In line with researchers' duty to protect confidentiality through seeking consent, the NHSIC state that participant consent must be provided at the time of requesting the data. If it is not possible to seek consent then 'Section 251 approval' must be obtained and sent with the data request (HES 2012a).

'Section 251 approval' (also called 'Section 251 support') refers to Section 251 of the NHS Act 2006. Section 251 support 'permits the common law duty of

confidentiality [and thus the seeking of participant consent] to be set aside so that information which identifies patients can be used without their consent' (NIGB 2012a). It is sought from the Secretary of State for Health through the Ethics and Confidentiality Committee (ECC), part of the National Information Governance Board (NIGB) (NIGB 2011a).

To obtain section 251 support, the criteria set out in figure x.x have to be met (NIGB 2011a):

Requirements for Section 251 support under the NHS Act 2006:

- The research has to be for a medical purpose; and
- The reason for using the information has to be for the purpose of improving patient care OR in the public interest; and
- The purpose cannot be achieved using de-identified data; and
- Seeking consent for the use of identifiable data is not practicable.
- The ECC need to be satisfied that the reason for needing the information is of sufficient quality, and of benefit to the public, to justify disclosing the information. They also need to accept that the use of section 251 is necessary and the reason for using the information cannot be achieved by taking a different approach.

The purpose of this thesis is to examine the relationship between multisite pain and falls in older people. This will provide the first steps that will ultimately result in an improvement of patient care for older people. Therefore, the information required was for a medical purpose, with the primary interest in improving patient care.

Identifiable data was required to access the HES and ONS data and achieve linkage with NorStOP survey data. De-identified data would not enable

information relating to specific individuals to be released. Moreover, de-identified aggregate level data (for example, total counts of exposures and outcomes within a population) would not enable allow the impact of putative mediating factors to be measured.

Seeking consent for the use of identifiable data was not possible due to impracticalities and the associated financial and bureaucratic costs. Finally, if identifiable information is not used then the relevant HES and ONS data could not be extracted or linked with NorStOP data. Thus, the proposed research objectives could only be achieved through using identifiable information to access and link HES and ONS data.

To summarise, the application to obtain HES and ONS data required section 251 support, which was be sought from the NIGB. The NHSIC stated that all requests for sensitive information are referred to the Ethics and Confidentiality Committee (HES 2012b), a branch of the NIGB. Therefore an application to the ECC will be made for consideration of section 251 support and an evaluation of the sensitive data required for the proposed research. The application to the ECC for section 251 support, hereafter referred to in the thesis as 'the NIGB application', thus required a carefully considered justification for data use without participant consent, particularly in the case of NorStOP participants who dissented to medical record review.

6.3.5 How a dissent from 'medical record review' is to be applied to the process of obtaining ONS and HES data

A fundamental principle of ethical research is obtaining valid participant consent. Equally, a decision to dissent from research participation must be respected to fulfil the duty of confidentiality. This raises some interesting questions around the position of respondents who dissented from 'medical record review'. An argument to support or reject the notion that the dissent from medical record review at baseline NorStOP is an 'absolute' was developed in order to justify the application for section 251 support for *all* NorStOP participants. This was achieved through reviewing the literature and undertaking a Patient and Public Involvement (PPI) consultation, processes which are now described.

6.3.6 Literature review: using personal identifiable sensitive data without consent

6.3.6.1 Aims and objectives

The objective of the literature review was to identify evidence examining the use of identifiable data without consent.

6.3.6.2 Methods

Medline, Embase, Cinahl and HMIC were searched using the terms displayed in 1 the search was limited to title and abstract. Terms within groups (denoted by each row in table x.x) were combined using the Boolean operator 'OR' and then each group was combined with the Boolean operator 'AND'. This search revealed 14 articles, all of which had their full text reviewed by VW.

Table 1: search terms

	Search terms
1.	Identifiable OR sensitive
2	Information OR data
3.	Research
4	Participant OR patient OR individual
5	Consent OR dissent
6	Without OR no OR unable

Publications from such governing bodies as the General Medical Council, the Medical Research Council, the Department of Health, the NIHR and the Academy of Medical Sciences were searched. The electronic database from the NIHR 'Involve' group, a national advisory group that supports greater public involvement in research (NIHR 2012a), was also searched (NIHR 2012b). References of retrieved articles were hand-searched. Three further relevant articles were obtained in addition to those obtained from the database search.

6.3.6.3 Narrative review

The majority of the literature was commentary and opinion pieces; four studies were designed to explore the issue of using identifiable (and sensitive) data without consent. Historically, the interpretation of the Human Rights Act 1998, the Common Law Duty of Confidentiality and the Data Protection Act 1998 by agencies governing access to data for research purposes (for example, the Patient Information Advisory Group, PIAG) proved challenging to researchers wishing to use previously collected health data (Academy of Medical Sciences, 2006; Souhami 2006). This situation largely arose from a lack of knowledge of public

opinion towards using identifiable data in research. Prior to this, only one study, a cross-sectional survey by Barrett e al (2006) had been published. Barrett et al (2006) interviewed the British public on their views towards the use of personal data by the National Cancer Registry without individual consent (Barrett et al, 2006). From the 2872 interviewed (response rate 65.5%), 72% did not consider inclusion of postcode, name and address in the Registry and subsequent use without consent for identification of potential participation in research to be an invasion of privacy; 2% of the sample however did consider this a privacy invasion (Barrett et al, 2006). In 2006, The Academy of Medical Sciences published a report into the use of personal data for public good; it concluded that more work needed to be undertaken to explore the public's views towards use of identifiable data without consent and that agencies controlling access to data must consider the greater public interest that research may bring in their balancing of benefits and harms relating to approving requests for permission (Academy of Medical Sciences, 2006).

Since the recommendations were made in 2006, two studies of public opinion have been completed. In 2009, the Department of Health commissioned a consultation to explore the issues around patient consent and confidentiality in relation to using their medical data for research (Knight 2009). Three in five respondents thought that researchers should be able to search patients' notes to find people who might be approached to take part in research and half of these thought this should happen after permission is granted from the PIAG (Knight 2009). Despite this finding, the report concluded "it is clear that the public expects their consent to be sought if the data used is identifiable" (Knight 2009). Finally, Buckley et al (2010) conducted a survey of 1575 members of the Irish general

public. Achieving a response rate of 40%, the majority of respondents felt that having prior consent agreements in place with the GP would allow the GP to share anonymous information with researchers without the need for study-by-study consent (Buckley 2010). One further publication of interest was a reflection upon lessons learnt of processing identifiable data without consent during the development of a disease register (Haynes 2007). Explicit consent was not sought for practical reasons, however public awareness of the register was 'ensured' though the sending of information leaflets to all local residents (30,000) detailing the register, how identifiable information will be used and how to withdraw from the register. The register was also advertised in local and national newspapers and leaflets were placed in general practices and local hospitals explaining the use of personal information and how to withdraw from the register. The researchers received no expression of desire to have their data withdrawn from the register, suggesting that the public were implicitly satisfied with the use of their identifiable data without consent (Haynes 2007).

It is clear from the literature summary that the public seem to generally accept the use of identifiable data for secondary research purposes providing it is within a framework of secure data and permission has been obtained from a central agency.

As for the problem of how to tackle the participants who dissented from medical record review, no specific advice in the literature can be applied to this situation. It seemed that the ECC may consider a dissent at NorStOP baseline to be an absolute dissent to any form of medical record review, however clinical experience dictates otherwise. Patients change their mind according to the context; indeed, the GMC (2008) state that consent is time, place and situation specific. Public and

patient involvement (PPI, or 'user involvement') was thus undertaken to explore the public's views towards using identifiable health care data and accessing HES and ONS data in patients who previously dissented from primary care medical record review.

6.3.7 Patient and public involvement

6.3.7.1 The role of patient and public involvement in research

Patient and public involvement (PPI) is also known as 'user involvement' (Involve 2012). 'The public' means patients, potential patients, service users, carers and organisations that represent people who use services (Keele 2009). 'Involvement' is defined as "active involvement where the people involved are not subjects" of research but are active participants. This means that research is carried out with and by members of the public rather than to, about or for them" (Hanley 2004). PPI can help to define what is ethically acceptable in research (Staley 2012); its importance is underlined through its integration into applications to Local Ethics Committees (Tarpey 2011). The host Research Centre are "committed to taking an explicit and systematic approach to involving the public in research" and therefore have a well-established framework for PPI (Keele 2009) including a Research Users' Group (RUG).

6.3.7.2 Aims and objectives

The aim of PPI was to explore the acceptability of using identifiable data to access HES/ONS data, and to link HES/ONS data to NorStOP survey responses for participants who dissented from primary care medical record review. Specific objectives were to explore the PPI groups views on the following:

i) *The risks, burdens and benefits to participants of using identifiable data without consent*

ii) *Whether the use of identifiable data without participant consent is acceptable for proposed thesis study*

6.3.7.3 The PPI process

This section provides a brief overview of the processes involved with PPI.

There are three different approaches to public involvement in research: consultation, collaboration and user-controlled (Involve 2012). A consultation process, whereby members of the public are asked for their views which are then used to inform decision making (Involve 2012) was undertaken to explore views towards using identifiable information without consent. The mode of public consultation can range from informal meetings, structured focus groups or one-to-one interviews (Involve 2012). Since PPI formed an integral part of the research proposal, a formal systematic approach was taken to ensure that the views sought were after careful consideration of all related issues under minimum researcher influence. The PPI was therefore developed using a focus-group format as a guide rather than relying on a more informal 'group chat' approach.

Focus groups are a 'form of group interview that capitalises on communication between research participants in order to generate data' (Kitzinger 1995: 299). Compared with one-to-one interviews, focus groups have the advantage of the 'safety in numbers' approach, which encourages respondents to reveal their thoughts (Kitzinger 1995). However, the potential for hierarchies to form within the

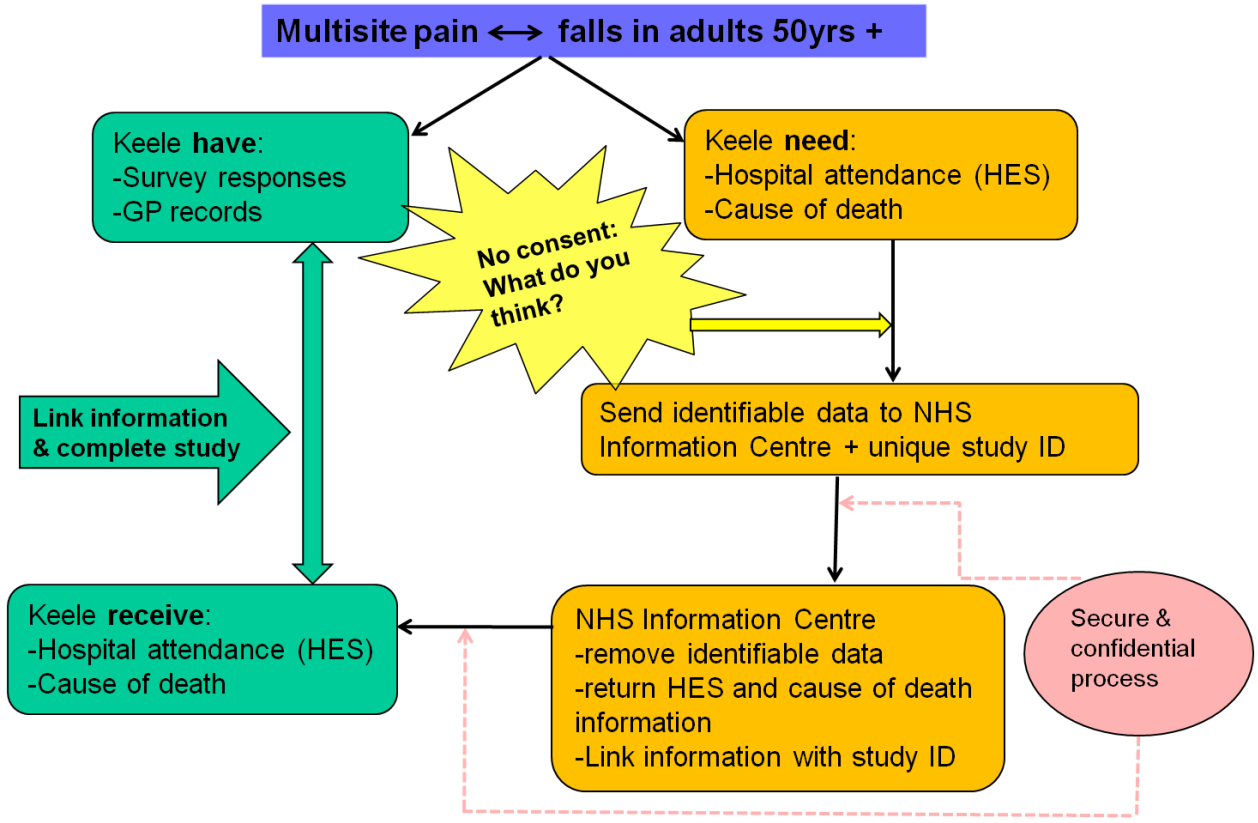
group and the negative impact on group dynamics and willingness to disclose opinions must be considered (Finch & Lewis 2003).

The PPI group were drawn from the existing RUG. Five group members were requested and no specific background demographics (for example sociodemographic status, health conditions) were required.

Participant invitation letters and information sheets were prepared, mindful of the need to write in language understandable to the lay public, avoiding jargon and providing clear simple explanations of the problem (Involve 2012).

The invites and information sheets were sent out two weeks prior to the meeting date to allow additional time for people to read the information (Involve 2012). This information contained a diagram to summarise the challenge requiring discussion, as figure 1.

Figure 1: ethical dilemma



6.3.7.4 PPI findings

The group discussed their concerns around accessing data without consent and were primarily concerned with the media coverage of missing or stolen personal information. The group highlighted the potential for participant distress if particularly 'sensitive' health information, for example HIV status or past history of termination of pregnancy, were shared non-confidentially and also raised concerned about the 'identifiability' of participants in related study publications. Concerns over using identifiable data and accessing HES and ONS data for participants who have already dissented from medical record review were raised by two group members at the outset of the meeting. A discussion about the original consent procedure and the nature of ONS and HES data compared with primary care records followed and the group reached an agreement that it was

acceptable to use identifiable data to access and link HES and ONS data to survey responses for participants who did not consent to medical record review because the information sought was different from that implied in the original study (i.e. primary care records) and dissent was not specific for the purposes outlined in the proposed research.

6.3.7.5 Strengths and limitations

The purpose of the PPI was to explore consumer views towards the use of identifiable data without consent using a focus-group format. Although not a formal qualitative research approach with respect to participant sampling, themes including scepticism towards data use and concerns over data security were explored using group dynamics to facilitate disclosure of views. It is therefore appropriate to consider the limitations of using such a methodology in the context of qualitative research.

Firstly, the participants were purposively sampled according to their availability on the meeting day. This obviously excludes those working during the scheduled meeting time, those unable to travel, and those with other prior commitments. The written correspondence in English and the meeting format also precluded non-English speakers and those with low literacy skills. However, the purpose of qualitative research is not to obtain an overall 'representative' view, rather to obtain an in-depth understanding of the experiences of particular groups or individuals. This in-depth understanding derives from the selection of respondents that fulfil the criteria for group inclusion while appreciating the range of experiences of those individuals (Greenhalgh & Taylor 1997). Therefore, the PPI members did meet the inclusion criteria (free on the scheduled meeting date, able

to understand and communicate in English and travel to the meeting venue) and ranges of experience including underlying medical problems and previous occupation were taken into consideration. For example, one member previously worked in the NHS and her different approach to the problem was appreciated, for example her “inside knowledge” of record storage and information sharing.

The possibility of the Chair (VW) influencing views was considered. The Chair interjected as little as possible, only contributing to clarify policies and procedures and to keep the discussion on track, thus keeping the potential to influence views to a minimum. The group dynamics worked well as all members were engaged equally in the discussion and respected each other’s opinions, perhaps as a result of having sat together on PPI panels before.

6.3.7.6 Summary of findings from PPI exercise

In summary, the group all agreed that using identifiable information without participant consent to access and link HES and ONS data was acceptable, and that this was also acceptable for participants who dissented from medical record review. Regarding the use of identifiable data without consent, these views are generally reflected in the literature. As discussed, the survey by Knight (2009) found that permission to use identifiable data without consent should be granted after review from the PIAG, who ensure the researchers have rigorous data security and confidentiality policies in place. The PPI has also added a new dimension to the literature. The PPI group felt that dissent from medical record

review, in some cases as long as ten years ago and inferred to be referencing primary care medical records, cannot be equated to a dissent to use of identifiable data to access and link HES and ONS data today. This is because primary care and HES/ONS data are different, the consent during NorStOP was not specifically for the proposed use and that there are strict policies governing data handling, security, storage and confidentiality policies in place.

6.3.8 Literature review and PPI impact upon data acquisition applications

The literature relating to public opinions of identifiable data use without consent was sparse. The PPI undertaken for the proposed study agreed with the published literature by finding that, in general, use of identifiable data for research without consent is acceptable providing adequate safeguards to protect confidentiality and data security are in place. The situation regarding a previous dissent to medical record review is a trickier concept. There is no published research to draw upon and bodies including the GMC state that consent is time, place and situation dependant. The PPI felt that was is acceptable to apply for HES and ONS data for participants who declined medical record review and this is the stance that was taken for the LREC, NIGB and HES/ONS data applications. The application also highlighted that section 251 support was *not* sought to override participant dissent to primary care medical record review as this is already in place and would amount to a neglect of duty of confidentiality and thus poor ethical practice.

Therefore, section 251 support was sought to use identifiable data without consent for all NorStOP participants to enable access and linkage of HES and ONS data with NorStOP survey responses, and in the cases of those who consented for

medical record review, with primary care records too. The mechanisms protecting participants' right to dissent were also highlighted.

The National Information Governance Board and Ethics and Confidentiality Committee verdict

The NIGB verdict was received on 20th September 2012. The Secretary of State for Health has determined that the application should be approved for access to those who have previously provided consent for medical record review. Therefore, section 251 support has been recommended to enable identifiable data to be used to obtain and link HES and ONS data for NorStOP participants who originally consented to medical record review. 4666 respondents will not have their survey data linked to HES and ONS; this may represent a missed opportunity given the PPI findings and the conditional nature of consent. The justification of the decision described in the correspondence did not include any evidence base or consideration of the PPI work undertaken. Unfortunately, due to the considerable length of time that this data acquisition had taken to date (the actual linked data was not received until May 2013), an appeal of the decision would not have been feasible.

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Appendix 6: Ethical approvals and conditions:

a) Approval From North Staffordshire Local Research Ethics Committee
b) Conditional approval from the National Information Governance Board
c) Condition of approval: poster to be displayed in NorStOP practice waiting rooms to inform respondents of further use of their data and to remind of dissent from reseach process
d) Approval from the National Information Governance Board

NHS
Health Research Authority

National Research Ethics Service

NRES Committee West Midlands - Staffordshire
HRA NRES Centre Manchester
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Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7815
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18 July 2012

Dr John McBeth
Reader in Chronic Pain Epidemiology
Keele University
Arthritis Research UK Primary Care Centre
Primary Care Sciences, Keele University
Keele, Staffordshire
ST5 5BG

Dear Dr McBeth

Study title:	**Multisite pain and falls in older people**
IRAS Project Number	**94842**
REC reference:	**12/WM/0200**
Protocol number:	**DRF-2011-04-147**

The Research Ethics Committee reviewed the above application at the meeting held on 11 July 2012. Thank you for attending to discuss the study.

Ethical opinion

Ethical issues raised by the committee in private discussion, together with responses given by the researcher when invited into the meeting.

1. The committee requested a brief outline of what the study involved and what its aims were.

   You stated that it is being carried out for a doctoral project for a GP. The study is attempting to identify why older people with chronic multi-site pain fall more often and explore the reasons behind this.

2. The committee queried how will the various databases link together and answer the research questions. The committee also queried what the procedure is for consenting participants and what happens to NorStOP participants who did not consent for their data from the study to be linked to their GP records.

   You stated that you would not be linking the NorStOP data to GP data for participants who did not consent for this. You clarified that NorStOP consisted of

approximately eighteen thousand participants; all aged over fifty, who provided self-reported data on pain, psychological outcomes and falls. Around 75% of these participants who agreed for their data to be linked to their GP Records have been used to populate two databases (PIPCA and CIPCA). You stated that in this study they wish to link these two databases to Hospital Episode Statistics (HES) and ONS data to explore the links between falls and multi-site pain. You are seeking to link HES as some falls will bypass primary care and otherwise would be missed. The aim of linking with ONS data is to examine whether the baseline data links to mortality rates.

3. The committee queried what you hope to get at the end.

   You stated that one of the most common causes of GP consultations is pain. You wish to see if there is a link between the people who attend their GP for pain and falls. You also stated you wish to attempt to identify the risk of falling in people.

4. The committee queried whether there is sufficient statistical input into the project.

   You stated that you have several high powered statisticians on board at Keele University. You will be using an established methodology but it is novel in this field. You stated that you are attempting to identify factors related to falls. You stated that Victoria Welsh will be supervised by Dr Kelvin Jordan and Dr Elaine Thomas as well as himself.

5. The committee noted that pain is specific to individuals and different forms are caused by different things. The committee also noted that there can be many different reasons for falling and queried with so many variables in the data will anything usable come out.

   You stated that in the over 50's around 10% of pain is not musculoskeletal pain. You are looking at the other 90% of pain which is musculoskeletal. You stated that there is a correlation between having a joint disease and having pain elsewhere. You also stated that they are considering chronic pain as a symptom leading to falls not as a cause, as US studies have shown that there are unidentified causes that can lead to falls. You stated that you wish to develop explicit models to identify the pathways that lead to falls; this will include co-morbidities and medication. You stated that the catch all group termed multi-site pain is overlaid by other groups.

6. The committee queried whether it will be possible to identify these other groups.

   You stated yes to a certain degree. You stated that the plan is to explore the relationship between pain and falls and statistically factor in other causes such as cognitive failure. You will first look at the strength of the relationship between pain and falls. You will then remove a certain cause (such as cognitive failure) and then see if the relationship is still there.

7. The committee queried whether NorStOP looked at osteoarthritis only.

   You clarified that NorStOP was sent to everyone over fifty. The aim was to identify osteoarthritis but looked at a broad range of questions. It measured anxiety, depression, cognitive functioning social networks and participation. They tried to cover as many things as possible that could be used to identify osteoarthritis.

8. The committee queried whether consent to access hospital records was given during NorStOP.

   You stated no, that is why you are applying to the NIGB for section 251 approval.

9. The committee queried whether consent was given to access the research data for future studies.

   You stated yes.

10. The committee queried why you don't ask the participants for consent.

    You stated that it would not be feasible as a large number would either have left the area and no longer be traceable or would be deceased now. You stated that section 251 approval from the NIGB will allow you to access the HES and ONS data.

11. The committee queried how the data is linked together if it is all anonymised.

    You explained the various processes and centres involved and informed the committee that the data would be anonymised.

12. The committee queried whether the researchers are assuming a correlation between pain and falls or if they are assuming cause and effect.

    You stated you could use a number of criteria to determine this. You stated that you will use Hill criteria to establish causality and that you have to assume a causal model.

13. The committee noted that the insurance indemnity provided expires on 31 June 2012 and a new certificate will need to be provided after this date.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, **subject to the conditions specified below**.

However: The committee expressed concerns that the researchers would be unable to extract the extra factors from the data – a point also noted in the peer review (Reviewer #2's comments).

The committee was concerned that imposing an outside model on the existing data-set could lead to incorrect conclusions

The researchers are advised to consider these points.

The committee nominated the co-ordinator to be the point of contact should further clarification be sought from the applicant upon receipt of the decision letter.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the

start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		15 June 2012
Evidence of insurance or indemnity	Professional Indemnity Insurance Certificate - Lockton	21 July 2011
Investigator CV	John McBeth	
Investigator CV	Christian Mallen	
Investigator CV	Victoria Welsh	
Letter from Sponsor	Keele University	15 June 2012
Other: NorStOP 1 Ethical Approval: 05/Q2604/20		15 August 2007
Other: NorStOP 1 Ethical Approval: 05/Q2604/72		15 August 2007
Other: NorStOP 1 Ethical Approval: 06/Q2801/90		21 July 2009
Other: Letter from NIHR		
Other: Research Contract		
Protocol	7	15 June 2012
REC application	3.4	19 June 2012
Referees or other scientific critique report	Scientific review from Arthritis Research UK	
Summary/Synopsis	1	15 June 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research

Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WM/0200	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Signed on behalf of:
Dr Kathryn Kinmond
Chair

Email: ashley.totenhofer@northwest.nhs.uk

Enclosures:	*List of names and professions of members who were present at the meeting and those who submitted written comments*
	"After ethical review – guidance for researchers"
Copy to:	Dr Victoria K Welsh - Keele University
	Professor Christian Mallen - Keele University
	Rhian Hughes - Keele University
	NIGB Ethics & Confidentiality Committee Secretariat

NRES Committee West Midlands - Staffordshire

Attendance at Committee meeting on 11 July 2012

Committee Members:

Name	Profession	Present	Notes
Miss Nicola Brooks	Solicitor	No	
Mr Michael Dale	Retired	Yes	
Mr Robert Edgar	Engineer (Retired)	Yes	
Mrs Shirley Ann Goldstraw	Lecturer in Midwifery	No	
Dr Mark Gunning	Consultant Cardiologist	No	Vice-Chair
Dr Jackie-Anne Kilding	Community Paediatrician	Yes	
Professor Paul Kingston	Professor of Ageing and Mental Health	No	
Dr Kathryn Kinmond	Senior Lecturer	Yes	Chair
Dr Aswath Kumar	Consultant Paediatrician	Yes	
Dr Arabinda Kundu	Head of Contraceptive & Sexual Health Service	No	
Mrs Meena Nachiappan	Company Secretary	Yes	
Dr Laofe Oladele Ogundipe	Consultant Psychiatrist	No	
Dr Sandie Sandbrook	Senior Lecturer	Yes	
Mr Victor Scofield	Legal Advisor, Banking (Retired)	Yes	Alternate Vice-Chair
Professor Monica Spiteri	Consultant Physician	No	

Also in attendance:

Name	Position (or reason for attending)
Mr Ashley Totenhofer	Acting Co-ordinator

NIGB
Ethics and Confidentiality Committee

Dr John McBeth
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18 September 2012

Dear Dr McBeth

ECC 6-02(FT1)/2012 Multisite pain and falls in older people

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions. This application was considered via the fast track process under criteria 4; time limited access to undertake record linkage/validation and to pseudonymise the data

Secretary of State decision

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined that the application should be provisionally approved for access to those who have previously provided consent for medical record review.

Context

This research application from Keele University requested access to confidential patient information in order to carry out linkage with data already extracted from GP practices and HES and ONS data. All participants had previously completed questionnaires as part of a previous study called the NorStop study, and for some this included consent being provided for review of medical records. Confidential patient information would be provided to the University by GP practices and this data would be used to request HES and ONS data for all patients. Date of birth, postcode and NHS number would be required to carry out linkages; however analysis would be carried out using anonymised data only.

ECC advice

Members considered this application to have clear public benefit, and noted that identifiable data would be used for a short period of time in order to carry out linkages. It was discussed that seeking specific consent for this data linkage would not be feasible considering the large cohort involved and the retrospective nature of the study. In addition it was noted that many of the cohort had originally consented for the review of their medical records.

Previous consent

Members discussed those instances where patients had not provided consent for original medical record review; the applicant confirmed that this was the case for 4666 patients. Members noted the assertions that consent was time, place and situation specific and that it would therefore be difficult to assume that dissent for primary health care record review given 10 years ago would mean dissent to HES and ONS linkage today. Members discussed whether this assertion was correct; a view was raised that as this was an extension of the previous data collection the previous dissent could be considered to indicate dissent for data linkage for this activity. However, on balance, members noted that only those who had completed the questionnaire would have their data used, that those who did not provide consent 10 years ago had not actively dissented and that the research team would only have time limited access to identifiable data.

Members requested further confirmation that those who had actively dissented via their GPs would not be included in the data linkage. The applicant confirmed that this was the case.

Fair processing requirements

Members agreed that patient information should be displayed within GP practices in order to ensure that the fair processing requirements of the Data Protection Act were met and to ensure that patients could register dissent with their GPs in relation to the current activity.

ECC advice conclusion

Members agreed that support should be recommended for this activity, subject to the following conditions of approval:

Conditions of approval

1. Confirmation of satisfactory security arrangements. Please note there has been a change to the security review process. Please review the following link (http://www.nigb.nhs.uk/s251/forms) which sets out the change, and please follow the guidance given. If you have any queries over this, please contact the Exeter Helpdesk.

2. Confirmation of a favourable research ethics committee opinion. **(received)**

3. Patient information should be displayed in participating GP practices with adequate opportunity for patients to opt out of the processing.

Further actions

Please confirm your acceptance of the above conditions and liaise with the Exeter helpdesk to complete the security assurance, final confirmation of your approval can be issued.

Please do not hesitate to contact me if you have any queries regarding this letter.

Yours sincerely

Claire Edgeworth
NIGB Deputy Approvals Manager

Ethics and Confidentiality Committee

Standard conditions

The favourable recommendation provided by the NIGB Ethics and Confidentiality Committee to the Secretary of State for Health is subject to the following standard conditions.

The applicant will ensure that:

1. The requested patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and that there is no disclosure of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent of the Secretary of State is facilitated and supported.
8. The wishes of people who have withheld or withdrawn their consent are respected.
9. The NIGB Office is notified of any significant changes that impact on the details of the application considered by the Ethics and Confidentiality Committee.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter. Details are available on the NIGB website.
11. Any breaches of security around this particular flow of data should be reported to the NIGB within 10 working days, along with remedial actions taken.

Keele University

Attention: NorStOP research participants who gave permission for medical record review

Multisite pain and falls in older people

✓Between 2002 and 2005, you took part in the North Staffordshire Osteoarthritis Project (NorStOP) and gave permission to researchers to review your medical records.

✓We, the researchers, are now extending the NorStOP studies by exploring the link between pain and falls in older people. This will help us to develop care packages to prevent older people with pain from falling.

✓We have permission from the NHS to link your NorStOP survey answers with basic information about your hospital attendances (cause of admission and duration of admission).

✓In order to make the link, we need to send your date of birth, NHS number, postcode and sex to the NHS Information Centre who hold your information. There are strict rules in place that mean your data will remain protected, secure and confidential at all times.

✓Once the hospital attendance information has been linked, all information that identifies you will be removed by the NHS Information Centre.

✓The linked information that we will use to study pain and falls will be anonymous. Strict rules ensure that this information is stored securely and confidentially.

✓If you would like to opt out of this research, please talk to the practice staff.

✓For further queries, please contact Dr Victoria Welsh on 01782 733905 or primary_care_sciences@keele.ac.uk.

Arthritis Research UK | primary care centre

NIGB

Ethics and Confidentiality Committee

Dr John McBeth
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Keele University
Keele
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80 London Road
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Tel: (020) 7004 1539
Email: ecoapplications@nhs.net

20 December 2012

Dear Dr McBeth

ECC 6-02(FT1)/2012 Multisite pain and falls in older people

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions. This application was considered via the fast track process under criteria 4; time limited access to undertake record linkage/validation and to pseudonymise the data

Secretary of State decision

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined that the application should be approved.

This final approval letter should be read in conjunction with the outcome letter dated 18 September 2012.

Context

This research application from Keele University requested access to confidential patient information in order to carry out linkage with data already extracted from GP practices and HES and ONS data. All participants had previously completed questionnaires as part of a previous study called the NorStop study, and for some this included consent being provided for review of medical records. Confidential patient information would be provided to the University by GP practices and this data would be used to request HES and ONS data for the entire cohort. Date of birth, postcode and NHS number would be required to carry out linkages; however analysis would be carried out using anonymised data only.

NIGB

Ethics and Confidentiality Committee

ECC conclusion

Members agreed that support should be recommended for this activity, subject to the following conditions of approval:

Conditions of approval

1. Confirmation of satisfactory security arrangements. **Confirmed on 11 December 2012.**

2. Confirmation of a favourable research ethics committee opinion. **Received on 29 November 2012.**

3. Patient information should be displayed in participating GP practices with adequate opportunity for patients to opt out of the processing. **Condition accepted 29 November 2012, the patient information poster was provided to the NIGB office.**

As the above conditions have now been accepted and met this provide confirmation of your final approval. I will arrange for the register of approved applications to be updated with this information.

Annual Review

Please note that this recommendation is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements.

Important changes

Please note that the current administration of applications made under these Regulations by the NIGB Ethics and Confidentiality Committee is due to transfer to the Health Research Authority by 01 April 2013, therefore please be advised that arrangements might have changed by the time the next annual review is due. Such arrangements will be communicated on the NIGB website once known.

Please do not hesitate to contact me if you have any queries regarding this letter.

Yours sincerely

Claire Edgeworth
NIGB Deputy Approvals Manager

Ethics and Confidentiality Committee

Standard conditions

The favourable recommendation provided by the NIGB Ethics and Confidentiality Committee to the Secretary of State for Health is subject to the following standard conditions.

The applicant will ensure that:

1. The requested patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and that there is no disclosure of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent of the Secretary of State is facilitated and supported.
8. The wishes of people who have withheld or withdrawn their consent are respected.
9. The NIGB Office is notified of any significant changes that impact on the details of the application considered by the Ethics and Confidentiality Committee.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter. Details are available on the NIGB website.
11. Any breaches of security around this particular flow of data should be reported to the NIGB within 10 working days, along with remedial actions taken.

Appendix 7: The Charlson Comorbidity Index diagnostic categories and weightings & practical considerations

The Charlson Comorbidity Index considers 16 diagnostic categories and each category is defined a weight, for example 'metastic tumour' carries the highest weight of 6, and mild liver disease carries the lowest weight of 1; the table below provides disease categories and their weightings. Each respondent is scored according to the presence of the listed diagnostic categories as indicated by the READCODE in their medical records.

Charlson Diagnostic Category	Weighted score
Acquired Immuno-Deficiency Syndrome	6
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart disease	1
Dementia	1
Diabetes	1
Diabetes with complications	2
Hemiplegia and paraplegia	2
Mild liver disease	1
Moderate or severe liver disease	3
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Renal disease	2
Rheumatological disease	1
Cancer	2
Metastatic tumour	6

Reproduced from Khan et al, 2010

Multimorbidity: using the Charlson score

Khan et al. were contacted about their use of the Charlson score with the Clinical Practice Research Datalink (CPRD), a national dataset of anonymised primary care records (https://www.cprd.com/researchpractice/), Khan 2010). Nada Khan kindly provided the READ and Oxmis codes that correspond to the conditions outlined in the Charlson Index. 3155 codes were received; after hand searching and removing Oxmis codes (not applicable to the present thesis' data), 2535 codes were ready to be extracted from the primary care electronic records.

These codes were written in 7 character format. Each code was checked with a corresponding 5 byte (or character) format to ensure each matched. Some medical conditions in the primary care electronic records are only held in 3-byte format and so each 5 byte code was checked as a 3 byte code to ensure that, if the coding was extracted based on only 3 byte format, irrelevant diagnoses would not be included. This extensive check involved screening all the codes for each of the disease categories. A spreadsheet was created for each disease category and each code within each database was cross matched with the Clinical Terminology Browser and the electronic GP records. An additional column was added next to the code in each excel spreadsheet describing how many characters needed to be preserved in that code. For example, some codes were acceptable to reduce to 3byte as this is what was coded in the GP database and all codes under that subheading were included in the Charlson score. Some codes had to be longer, 4 or 5 byte, to ensure that irrelevant diagnoses were not captured in the subsequent merging process. Again, these were cross referenced with the GP data so it wouldn't miss any codes that were only 3 bytes long.

After the additional column in the spreadsheet detailing how many characters need to be preserved was created, the codes were then transferred to the statistical analysis package (STATA). A code was then written to truncate the original code into the required number of characters and the resulting databases were saved.

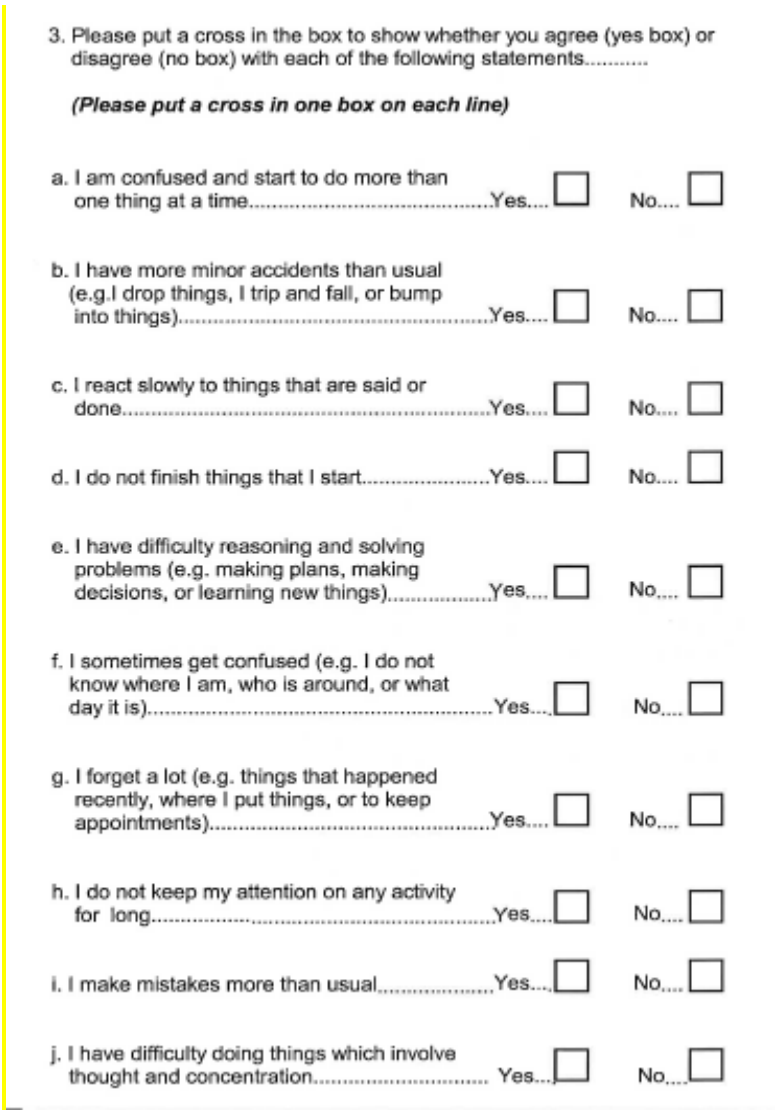
Each diagnostic category by has a list of the READCODES so a checking process must be in place to ensure that non-relevant conditions that would be included until a 3-byte code are not scored as a Charlson-defined diagnostic category. An example of the checking process is highlighted by the category 'AIDS', 5-byte READ code A788. . All codes with A788(x) are relevant to AIDs and should be included in the subsequent extraction process. It is not possible to shorten this search to A78.. as this represents 'other viral and chlamydial diseases', including verrucas and warts, which are not all relevant to the 'AIDS' diagnostic category. Therefore, the codes to be extracted relating to AIDS must all be of the 4 byte READcode otherwise the many thousands of codes relating to verrucas will be extracted and scored as a Charlson 'AIDS' category.

Another specific example to present in this Methods chapter is the READcodes used to extract ‘diabetes’ rather than ‘diabetes with complications’. Looking through the electronic GP records (ordered alphabetically according to diagnostic codes to facilitate hand searching), most diabetes is coded as C10F. (type II diabetes mellitus) or C10E (type I diabetes mellitus). However, 189 respondents were coded as C10.. , which is the overarching code for diabetes mellitus including type I and type II and any associated complications. From clinical experience, patients generally have more than one associated code for diabetes if they are experiencing complications, for example, one code for the disease itself (C10F.) and then specific codes for complications (C10F6 type II diabetes mellitus with retinopathy). Thus, in order to generate a command to score ‘diabetes without complications’ and a command to score ‘diabetes with complications’ without overlap, diabetes was scored using the 4 byte codes C10F and C10E and diabetes with complications was searched using 4 byte codes and excluding C10F and C10E. The patients with only 3 byte codes recorded had their records searched within the consultation database and coded as either ‘diabetes without complications’ or ‘diabetes with complications’.

The scores generated for each Charlson disease category were then added together and a combined score was given as the Charlson Comorbidity Index score, ranging from 0 – 33 theoretically, although the highest score within the GP consultation database was 8. All respondents with a final score of ‘missing’ were recorded with a score of ‘0’ since a missing score simply meant that there were no relevant consultations.

There are more than 2500 codes, these are available upon request from the author.

Appendix 8: ABS-SIP scoring used in the NorStOP survey



3. Please put a cross in the box to show whether you agree (yes box) or disagree (no box) with each of the following statements.....

(Please put a cross in one box on each line)

a. I am confused and start to do more than one thing at a time.....Yes.... ☐ No.... ☐

b. I have more minor accidents than usual (e.g.I drop things, I trip and fall, or bump into things).....Yes.... ☐ No.... ☐

c. I react slowly to things that are said or done.....Yes.... ☐ No.... ☐

d. I do not finish things that I start.....Yes.... ☐ No.... ☐

e. I have difficulty reasoning and solving problems (e.g. making plans, making decisions, or learning new things).....Yes.... ☐ No.... ☐

f. I sometimes get confused (e.g. I do not know where I am, who is around, or what day it is).....Yes.... ☐ No.... ☐

g. I forget a lot (e.g. things that happened recently, where I put things, or to keep appointments).....Yes.... ☐ No.... ☐

h. I do not keep my attention on any activity for long.....Yes.... ☐ No.... ☐

i. I make mistakes more than usual.....Yes.... ☐ No.... ☐

j. I have difficulty doing things which involve thought and concentration..... Yes.... ☐ No.... ☐

NorStOP General Health Questionnaire, adapted from

Bergner M, Bobbit RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Medical Care* 1981; 19: 787-805.

Appendix 9: Preparing the data for Cox's proportional hazard modelling

Firstly, the data has to be prepared to enable survival analysis. This involves the following steps:

i) The time period that each respondent has been in the study, from entry to exit needs to be defined. To do this, each NorStOP cohort needs to be split into two groups: (a) those who did not respond to three year follow up; and (b) those who did respond to three year follow up who did or did not respond to six year follow up. This enables dates to be assigned to each group:

NorStoP Cohort	Entry year	Exit year
N1 a	2002	2005
N1 b	2002	2008
N2 a	2002	2005
N2 b	2002	2008
N3 a	2004	2008
N3 b	2004	2011

ii) Date of entry needs to be defined: this is the baseline survey return date (variable name is DOE). This will be the same for the analysis for GP recorded falls and HES recorded falls.

iii) Date of exit needs to be defined: for those that didn't complete three year follow up (group (a)), the date of exit is the end of the survey distribution wave of three year follow up. For those that did complete three year follow up (group (b)), this is the end of the six year survey distribution wave.

This is because, for the GP and HES-linked data for NorStOP consenters to medical record review, patients are included until point of drop-out. Hence a non-responder at three year follow up has medical records collated until the end of three year follow up survey distribution mail out, at which point they are withdrawn from further follow up as a non-response and therefore withdrawn consent is registered. All responders at three year follow up have medical records to 6 year survey time point regardless of their response to six year follow up.

iv) Respondents who died during the follow up period i.e. their date of death (and thus exit from the study) preceded survey end point are censored. (Censoring occurs when there is incomplete follow up available. The variable 'date of death' was generated in a format compatible with date of exit and those who had a date of death preceding the date of exit were tagged.

v) Next, respondents who fell during the survival analysis study time period are identified i.e. those whose first GP or HES-recorded fall date lies between the date of entry and the date of exit.

vi) Finally, a date of exit needs to be generated for all respondents. This variable is '[GP/HES]fallDOExit' and it describes an exit point for all respondents, either the date leaving the survey at three year or six year follow up, or the date of a fall. Date of death is not included in this variable since it is taken account of in the command [censored].

vii) The data is then declared to be 'survival-time' using the *stset* command in STATA14 and the variables to include in the analysis are defined. This enables STATA to run data consistency checks to ensure that variables declared to be used in the survival analysis make sense. The following command is used for GP recorded falls where the 'scale' unit is defined as days (365.25) (HES falls are measured in the same way, replacing GPfall variables with HES fall variables):

stset GPfallDOExit, failure (GPfallinstudy) origin (DOE) id (surveyid) scale (365.25)

Appendix 11: Research output and contributions

Welsh V, Mallen CD, McBeth J. Data-linkage studies: the ethical challenges of using patient identifiable data without consent. Society of Academic Primary Care Annual Conference 2013, Nottingham [National; Poster].

Hughes R, **Welsh V**. Achieving the IGT for Hosted Secondary Use Teams. NHS-HE Jisc /JANET national meeting, hosted by the NIHR [National: Presentation (invited speaker)]

Welsh V, Mallen CD, McBeth J. Multisite pain and falls: a systematic review to identify putative mediating factors. North American Primary Care Research Group Annual Conference, New Orleans 2012 [International; poster]

National Institute for Health and Care Excellence Quality Standards Specialist Committee Member for Quality Standard 86: Falls prevention; 2017 update.

Appendix 11: Reflections on the thesis

Undertaking this thesis over the past six years, on a part time basis and with two gaps of maternity leave, has been an invaluable experience for my academic career development and on a personal level. I have learnt about the processes of grant applications, ethics applications and the legal aspects of using patient identifiable data without consent. Learning how to manage my time effectively and to work flexibly by reorganising the project timeline to enable the ethics and data applications to be completed as early as possible has been useful as I plan future research with an appreciation of the potential for unpredictable changeable requirements. I received formal training in systematic reviewing and meta-analysis, advanced epidemiology and statistics and have a sound understanding of how to use statistical software packages, all necessary in building my academic career. I can handle large databases and have a good depth of knowledge for working with big datasets that will be incorporated into future grant applications. I have learnt the value of patient and public involvement in research and will ensure that this process is included in future research design. The most significant lesson I have learnt is how academic and clinical medicine interact and complement each other; this appreciation has allowed me to ask questions for future research that have been derived from clinical practice and enabled me to become more focused upon ensuring my research truly impacts clinicians and our patients in a useful and meaningful way.

Reflecting upon what I might do differently, it would have perhaps been beneficial to design and conduct the questionnaire from the outset to enable the gold standard method of collecting data on self-reported falls (daily recording of falls

using a calendar) to be followed. It may have been useful to undertake a pilot study to explore fall-related codes in GP records prior to designing the study to then perhaps find ways to maximise capture of fallers requiring primary care. This might be done by analysing the full text of consultations and looking at which codes are most associated with having 'falls' documented in the free text (for example, 'abrasion' or 'soft tissue injury'). I would have used different questions to illicit information for potential confounders, for example asking specifically about multifocal spectacle use to then include this as a risk factor. Other risk factors that would have been useful to include are a history of urinary incontinence and poor sleep. Sensitivity analysis could have been employed to look at sub-groups and explore the potential influence of hidden biases. It would have been interesting to compare falls prediction models within thesis sample A and thesis sample B, since thesis sample B contained a higher proportion of those with fewer comorbidities, medications and physical limitations. Any differences between these thesis samples could potentially indicate that different groups of patients have different falls risk factors and that perhaps the current approach to falls prevention in which all patients undergo the same recommended multifactorial assessment might not be appropriate, that it might be possible to start to target falls assessments and that further work into this area is necessary.

Throughout the process of completing this thesis I have developed as an academic, a clinician and as a person and I look forward to taking the lessons I have learnt forwards into the next stage of my academic clinical career.